Implementation and Evaluation of Tailored Intervention Strategies to Influence Antibiotic Prescribing for Community-Acquired Pneumonia

by

Maher Ali Almatar, BPharmSc, MPharmSc

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Pharmacy, School of Medicine

University of Tasmania

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Abstract

Adherence to guidelines for the management of community-acquired pneumonia (CAP) has been shown to improve patients' clinical outcomes. However, several studies have indicated that the chosen antibiotic regimen is frequently not consistent with guideline recommendations. This might lead to suboptimal treatment, either by exposing patients to a greater risk of treatment failure or by unnecessary use of broad-spectrum antibiotics, which contributes to the emergence of antibiotic-resistant pathogens or consequent development of *Clostridium difficile*-associated diarrhoea. It has been demonstrated that active implementation of CAP guidelines can significantly improve adherence to recommendations, which consequently, might improve patients' clinical outcomes.

The present research developed, implemented and evaluated tailored intervention strategies to improve physicians' concordance with CAP guidelines. A number of inter-related studies were conducted as a part of this research project.

Firstly, baseline data was collected to measure the level of physicians' adherence to national CAP guidelines in two Tasmanian hospitals, the Royal Hobart Hospital (RHH) and North Western Regional Hospital (NWRH). It was evident in that study that adherence to CAP management guidelines was poor at both study sites (16.1% and 7.5% for RHH and NWRH, respectively).

This was followed by a study to identify and quantify potential barriers to the adherence to CAP guideline recommendations. A questionnaire was distributed to RHH doctors in non-surgical areas of practice. Of the study population, 43.1% doctors responded to the survey; of those who responded, 46.4% thought the influence of senior doctors on their juniors could be a factor affecting adherence to the guidelines. Other barriers noted were a lack of guideline awareness (39.3%), the requirement to calculate the severity of CAP (35.7%), and the

existence of other guidelines that conflict with *Therapeutic Guidelines*: antibiotic, version 14 (TG14; 28.6%).

A qualitative study was then designed to determine factors that influence doctors working within the emergency department (ED) to prescribe ceftriaxone outside the TG14 recommendations. Eight face-to-face interviews were performed with ED doctors. Five main themes emerged as influencing decisions regarding the selection of ceftriaxone for patients with CAP: (i) clinical intuition compared to a structured evaluation of severity, (ii) clinical uncertainty, (iii) prior clinical experience, (iv) source of guidance and (v) prescribing etiquette.

A questionnaire survey was then sent to infectious disease pharmacists nationally in order to identify the strategies that have been used and perceived as successful for the management of CAP in their institutions. Of the study population, 41 pharmacists (27.3%) responded to the questionnaire. Of these, 90.2% pharmacists reported their hospitals having an antimicrobial stewardship (AMS) program. Multifaceted strategies to enhance antibiotic prescribing in ED for CAP, were mentioned as being in place in all responses. However, the largest number of the respondents (34.1%) considered use of CAP clinical pathways to be the most effective strategy.

Intervention strategies were subsequently developed and implemented based on the findings from the above studies. Two interventions were implemented over two time periods: one with general strategies across medical units and a second focused on the ED. During the general intervention period, local CAP guidelines (based on TG14) were released. The guidelines were developed and approved by the hospital's medical and emergency departments. The release of the CAP guidelines was accompanied by a multifaceted educational package to increase awareness of the guidelines. Medical and ED teams were targeted in the educational package, which included group sessions, wall posters and

laminated lanyard cards summarising the local guidelines. During the second time period, two further strategies were introduced (a CAP clinical management pathway and monthly auditing with feedback) and targeted specifically at ED staff.

We evaluated the impact of the interventions on guideline adherence rates and clinical outcomes (mortality rates and hospital length of stay, LOS). To evaluate the impact of the intervention, two hospital sites were selected, one (RHH) acted as an intervention site and the other (NWRH) as a control site where no intervention was made. The study found the intervention had an overall impact on guideline adherence rates at the intervention site, and it reduced overall mortality rates and LOS for patients with non-severe CAP. Compared to the baseline data, the adherence rate increased significantly at the RHH during the intervention period (16.1% vs 50%; $p < 0.05$). However, no significant improvement was indicated in the control site (7.5% vs 19.1%; $p > 0.05$). The in-patient mortality was significantly lower in the intervention group when compared to the non-intervention groups (all baseline data plus the data from the NWRH during the intervention period) (3.4% vs 7.3%; $p < 0.05$). Sub-group analysis revealed patients with non-severe CAP in the intervention group had an average LOS 0.8 days shorter than the non-intervention groups ($p < 0.05$).

Results from the previous study indicated a positive impact of the intervention in the overall adherence to CAP recommendations. However, two main strategies were conducted in two consecutive times during the intervention periods, a general intervention and an ED-focused intervention. Therefore, a time-series analysis was conducted to determine the impact of strategies over time at the intervention site. The rates of adherence to the CAP guidelines during the pre-intervention (5 months) and general intervention periods (5 months) were 28.1% and 31.2%, respectively. The difference was not statistically significant. During the ED-focused intervention period (7 months), the level of adherence with guidelines was significantly higher at 61.5% ($p < 0.05$).

Finally, we evaluated the use of ceftriaxone in all indications in two time periods, before and after the initiation of the intervention. The aim of this study was to determine if our intervention in CAP management could affect the use of ceftriaxone in other indications. Concordance to the TG14 for all indications, with the exception of respiratory tract infection (RTI), was similar between the two study periods. For the RTI, concordant use of ceftriaxone significantly increased from 50% during the first period to 64.5% during the second study period ($p < 0.05$). Among community-acquired lower respiratory tract infections, our findings indicated a significant decrease in the unnecessary use of ceftriaxone for patients with mild CAP and acute exacerbation of chronic obstructive pulmonary disease in the intervention group (both 19% vs 3.2%; $p < 0.05$). However, there were no significant changes in the appropriate prescribing of ceftriaxone for other indications.

In conclusion, this research project identified, with in-depth analysis, potential factors that lead to the prescription of discordant antibiotic regimens for empirical management of CAP. It was subsequently demonstrated that a tailored multifaceted intervention significantly improved adherence to CAP guidelines, which consequently reduced the inappropriate prescribing of ceftriaxone for this indication. This was associated with a decrease in mortality rate and length of hospital stay among patients in the intervention group.

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Peer-reviewed Journal Publications

- Almatar M, Peterson GM, Thompson A, McKenzie D, Anderson T. Community-acquired pneumonia: why aren't national antibiotic guidelines followed?. *International Journal of clinical practice.* 2014.
- Almatar M, Peterson GM, Thompson A, Zaidi STR. Factors influencing ceftriaxone use in community acquired pneumonia: emergency physicians' perspective. *Journal of Emergency Medicine Australasia.*2014; 26 (6): 591-5.
- Almatar M, Zaidi STR, , Thompson A, McKenzie D, Anderson T, Peterson GM. Targeted clinical pathway and monthly feedback improve physicians' concordance to community-acquired pneumonia guidelines. *International Journal of clinical practice.* (under review).

Conference Abstracts

- Almatar M, Peterson G, Thompson A, McKenzie D, Anderson T. Antibiotic prescribing for lower respiratory tract infections: are guidelines being followed? *Australian Society for Antimicrobials annual meeting*. Brisbane, Australia, February 23 to 25, 2012.
- Almatar M, Peterson G, Thompson A, McKenzie D, Anderson T. Community-acquired pneumonia: why aren't national antibiotic guidelines followed? An Australian prospective. *13th Asia-Pacific Congress of Clinical Microbiology and Infection.* Beijing, China, October 25 to 28, 2012.
- Almatar M, Peterson G, Thompson A, McKenzie D, Anderson T. Community-acquired pneumonia: why aren't national antibiotic guidelines followed?. *Joint Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists-Australasian Pharmaceutical Science Association Conference.* Sydney, Australia, December 2 to 5, 2012.

- Almatar M, Peterson G, Thompson A, McKenzie D, Anderson T. Empirical use of ceftriaxone in the main tertiary hospital in Tasmania, Australia: a target to improve. *Australian Society for Antimicrobials annual meeting*. Sydney, Australia, February 21 to 23, 2013.
- Almatar M, Peterson G, Thompson A, McKenzie D, Anderson T. Multifaceted intervention to improve adherence to community acquired pneumonia (CAP) management guidelines. *National Medication Symposium. Brisbane,* Australia, May 21 to 23, 2014.

Abbreviations

ABR = antibiotic resistance

ACSQHC = Australian Commission on Safety and Quality in Health Care

AMS = antimicrobial stewardship

ATS = American Thoracic Society

BTS = British Thoracic Society

CAPTION = Community-Acquired Pneumonia: Towards Improving Outcome Nationally

CDC = Centers for Diseases Control and Prevention

CDI = *Clostridium difficile* infection

C difficile = Clostridium difficile

COPD = chronic obstructive pulmonary disease

CRE = Carbapenem-resistant *Enterobacteriaceae*

CAP = Community-acquired pneumonia

EBM = Evidence-based medicine

ED = emergency department

HAI: hospital-acquired infections

ICU = intensive care unit

IDSA = Infectious Disease Society of America

IECOPD = infective exacerbation of chronic obstructive pulmonary disease

IRVS = intensive respiratory support or vasopressor support

LOS = length of hospital stay

μg = microgram

MIC = minimum inhibitory concentration

mL = millilitre

Mmol/l = millimoles per litre

MRSA = methicillin-resistant *Staphylococcus aureus*

NH = nursing home

NWRH = North Western Regional Hospital

PSI = Pneumonia Severity Index

RHH = Royal Hobart Hospital

S Pneumoniae = *Streptococcus pneumoniae*

Spp.= species

TG = *Therapeutic Guidelines*

TG14 = *Therapeutic Guidelines* Version 14

UK = United Kingdom

US = United States

VRE = vancomycin-resistant *Enterococcus faecium*

WHO = World Health Organisation

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Chapter 1. Introduction

1.1. Antibiotics

The term "antibiotic" was firstly used in published papers in 1942 by Selman Waksman (1, 2). Since then, the term "antibiotic" has been used frequently in literature. In his article, Selman describe an antibiotic as *"a chemical substance, produced by microorganism, which has the capacity to inhibit the growth of and even to destroy bacteria and other microorganisms" (2).*

Prior to the introduction of antibiotics and vaccination into medical practice, infectious diseases accounted for over 30% of the overall human deaths (3). However the antibiotic era has been associated with a marked reduction in mortality and morbidity associated with infections, for example, death rates due to pneumonia and influenza decreased by 0.5% per year during the antibiotic era (3).

Historically, the modern antibiotic era started with the accidental discovery of penicillin by Sir Alexander Fleming in 1928 when he noticed that *Penicllium notatum* had destroyed staphylococcus bacteria in a culture plate (4), and since then, the course of medicine has been changed. This discovery was an avenue to other researchers to discover new antibiotics in the following years. It can be said that the period between 1950 and 1980 was the golden era of antibiotics, since most of the antibiotic classes in use today were discovered during that period (5).

Coates *et al.* argued that there are five main reasons behind the limited development of new antibiotic classes (6). The first of these is that the cost and risk of developing analogues of the existing antibiotic classes is far less than developing wholly novel agents. Developing new classes with broad-spectrum antimicrobial coverage is now more difficult than it was in the 20th century. Large scale investments by the pharmaceutical industry in genomic

approaches to find a new antibiotic class have also failed. Furthermore, difficulties in securing product registration have been a disincentive to industry investment. Finally, most pharmaceutical companies and universities have closed their departments working on antibiotic development, leading to deskilling in this specialised research area. According to a 2009 report, only five pharmaceutical companies still have an active development program for antibiotic discovery, namely GlaxoSmithKline, Novartis, AstraZeneca, Merck and Pfizer (7).

In recent years, concerns have increasing regarding the increasing rates of antibiotic resistance (ABR) (8). In this era of increasing emergence of ABR, development of new antibiotic classes, that are effective against known resistant microorganisms is crucial (9). As a response to this public health concern, the Infectious Diseases Society of America (IDSA) raised the awareness about the problems in 2004 with a big campaign called Bad Bugs, No Drugs (10). This campaign was followed by calls for global commitment to develop 10 novel antibiotics by 2020 in order to respond to the challenge of resistance (11-13). Furthermore, it has been suggested that in order to tackle resistance at least 20 new classes of antibiotics are needed every 50 years to keep antibiotics effective (6). However, the future of antibiotic therapy is still in doubt, as the drug development pipeline suggests that there will be few new classes introduced in the next two decades (Figure **1.1**) (14, 15). Therefore, until this situation is rectified, preserving the utility of the antimicrobial agents already in existence is essential (16).

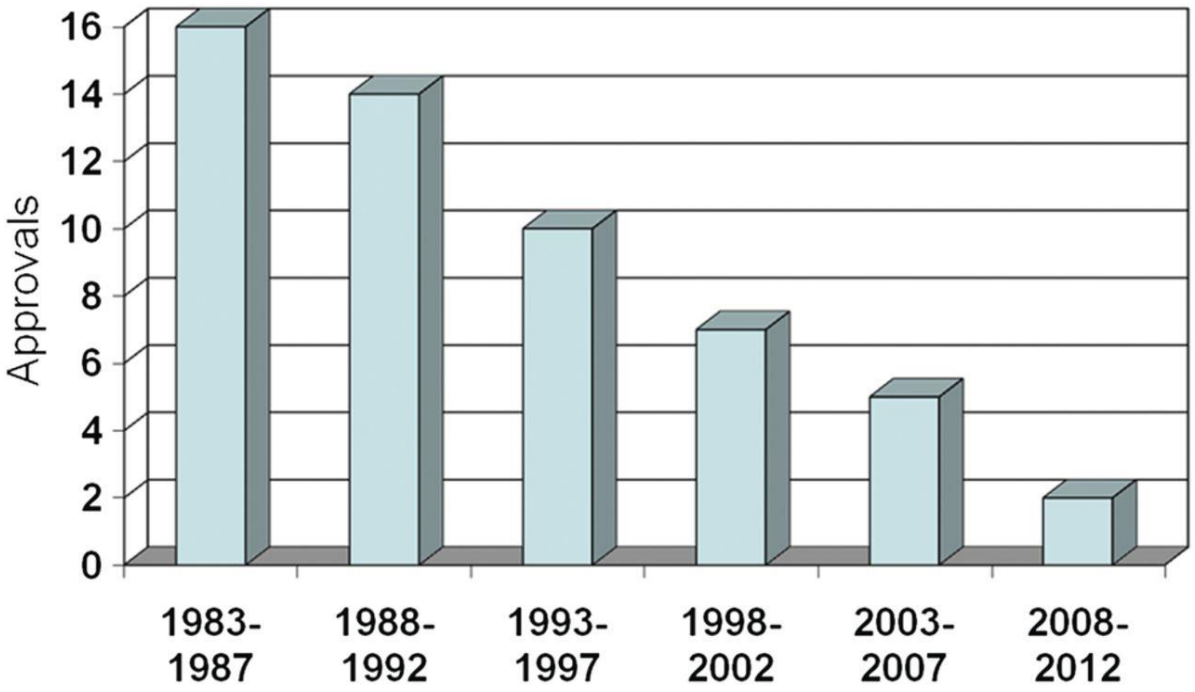


Figure 1.1: The number of newly approved antibiotic agents in the United States from 1983 to 2012 (17).

Data from several studies have identified a trend of increasing overall antibiotics use during the last two decades (18-22), with a significant shift toward prescribing of broader-spectrum agents (23-26). In their analysis of pharmaceutical sale data from 71 countries, Van Boeckel *et al.* concluded that there was a 36%increase in antibiotic consumption between 2000 and 2010 (27). Furthermore, it was estimated that global sales of antibiotics in 2009 generated $42 billion dollars and that there was a 4% annual growth rate (28). The increasing trend of antibiotic usage has raised major public concerns since it has been believed that the rise of antibiotic usage, particularly broad-spectrum antibiotics, has led to the increasing problem of resistant microorganisms (29, 30). Further details regarding this will be discussed in the next section.

1.2. Impact of inappropriate use of antibiotics

Inappropriate (non- adherence to recommended guidelines) or unnecessary use of antibiotics has been shown to be associated with increase mortality and worsen clinical outcomes due to preventable side effects such as allergic reaction, under coverage of the suspected microorganisms such as in the case of empirical treatment of an infection, and subsequent infections with resistant microorganisms or subsequent infections with *Clostridium difficile (C difficile* (31-34).

1.2.1. Adverse effects and antibiotics

Antibiotics account for almost 20% of all drug-related adverse effects that result in a presentation to the emergency department (ED) (35, 36). In a study that looked at ED visits related to antibiotic administration, Shehab et al. found that allergic reactions were the most common cause of antibiotic-related morbidity, accounting for 4 out of 5 of these presentations, wherein penicillins and cephalosporins were responsible for 50% of these events (36). In such cases, the symptoms may range from mild itching and rash to more serious skin reactions and breathing problems (37). Gastrointestinal adverse effects attributable to antibiotics have also been commonly observed. A review article of 415 publications that looked at the efficacy and tolerability of amoxycillin/clavulanic acid found that gastrointestinal adverse effect was the most reported adverse effect related to the use of this agent (38). A previous study has reported that 30% of the adverse effects related to third generation cephalosporins were gastrointestinal (39). The relationship between the use of some antibiotics, particularly aminoglycosides, and ototoxicity has been widely investigated (40, 41). Lerner et al. investigated the impact of gentamicin on the rate of ototoxicity in 54 patients, and they found that ototoxicity occurred in 11% of the patients who were treated with this particular aminoglycoside (42). Aminoglycosides, alongside vancomycin, have been considered as nephrotoxic agents (43, 44). In a study that looked at the prevalence of nephrotoxicity among

360 patients in intensive care units who were initiated with aminoglycosides, the authors found that 58% of the patients developed aminoglycoside-associated nephrotoxicity (43). Hence the suggestion that the best way to prevent these adverse effects is to avoid the unnecessary use of antibiotics (45).

1.2.2. *Clostridium difficile* infection (CDI) and antibiotics

C difficile is an opportunistic gram-positive anaerobic bacillus which is acquired through ingestion of material contaminated by faecal *C difficile* spores (46). *C difficile* can be transmitted by touching a contaminated area or via a person-to-person contact, such as other patients or even health care providers (47, 48). The spores resist stomach acidity and develop into vegetative bacteria in the small intestine (49). One of the most common reasons that would lead to the colonisation of *C difficile* and causing an infection is through disturbance of the normal intestinal gut flora (46). CDI may manifest in a range of forms, from asymptomatic, mild uncomplicated case to acute diarrhoea, which could be life threatening if not treated (49, 50).

Over the past few years, there has been a significant increase in the incidence of CDI globally and in Australia (51-56). Within Australian hospitals, for instance, the rate of hospital-identified CDI increased from 3.25 to 4.03 cases per 10 000 patient days between 2011 and 2012 (57, 58). A recent surveillance report from Tasmanian Infection Prevention and Control Unit has indicated an almost three-fold rise in the incidence of hospital-identified CDI across all Tasmanian acute public hospitals from 2.3 per 10 000 patient days in the third quarter of 2009 to 6.3 per 10 000 patient days in the first quarter of 2014 (52). The same report has indicated a similar increase in CDI at the Royal Hobart Hospital (RHH) from 2.1 to 6.4 per 10 000 patient days between the first quarter of 2009 and the third quarter of 2014. According to Mitchell *et al.*, the increase in the rates of the hospital-identified CDI among Tasmanian hospitals could be due to the increasing rates of the community-associated CDI as

observed in their study (59). One possible explanation of this increase, according to the authors, could be the possible increase of the use of antibiotic agents in the community.

The association between CDI and increased mortality rate has been examined extensively in the literature (60, 61). Studies have found that the mortality rate due to CDI has increased over the last decade (62, 63). For example, in the United States, it was found that CDI-related mortality rates increased almost five fold, from 5.7 per million populations in 1999 to 23.7 per million population in 2004 (62). In a systematic review article, Mitchell and Gardner have examined 24 case-controlled studies and found that infection with CDI was associated with in-hospital mortality rates ranging from 8% to 37.2% (64). The association between CDI and increased mortality rate has also been investigated in one Australian study (64). In their case-controlled study, Mitchell *et al.* showed that the mortality rate for patients with CDI was significantly higher than the control group at 60 days (12.6% vs. 6.3%), 90 days (14.6% vs. 7.3%) and 180 days (23.4% vs 9.2%). CDI has also been associated with prolonged LOS (57, 61, 65). Forster *et al.*, retrospectively investigated the impact of CDI on LOS in a Canadian teaching hospital for 7 years from 2002 to 2009 (66). It was shown from the study that patients who were admitted with CDI were more likely to stay longer than those without CDI (34 days vs. 8 days).

During the past decade, there has been an increasing amount of literature on the impact of CDI on healthcare costs as well (67-74). In one systematic review , the authors found that the estimated cost to treat patients with primary CDI ranged from $2,871 to $8,570 per case and, for recurrent CDI, the costs ranged from $13,655 to $18,067 per case (67). There are several factors that contribute to the high costs associated with CDI. These factors are associated with increased utilisation of healthcare resources, recurrent infection, treatment failure, and in particular an increased length of in-patient stay (68). Consistent with this, a retrospective observational study conducted by Al-Eidan *et al.* in 87 hospitalised patients with

CDI, found that 93.8% of the cost was related to the LOS, with the remaining 6.2% of the costs accounted for by laboratory tests and pharmacological therapy (75).

Antibiotic therapy has been considered as the main cause of CDI due to their effect on disturbing normal gut flora (Figure **1.2**). This has been supported by a large volume of published research that has examined the relationship between antibiotic usage and increased incidence of CDI (76, 77). In a systematic review of 48 studies regarding risk factors of CDI, Thomas *et al.* found that 41 studies indicated a positive correlation between antibiotic use and the incidence of CDI, with odds ratios ranging from 2.86 to 6.92 (76) .

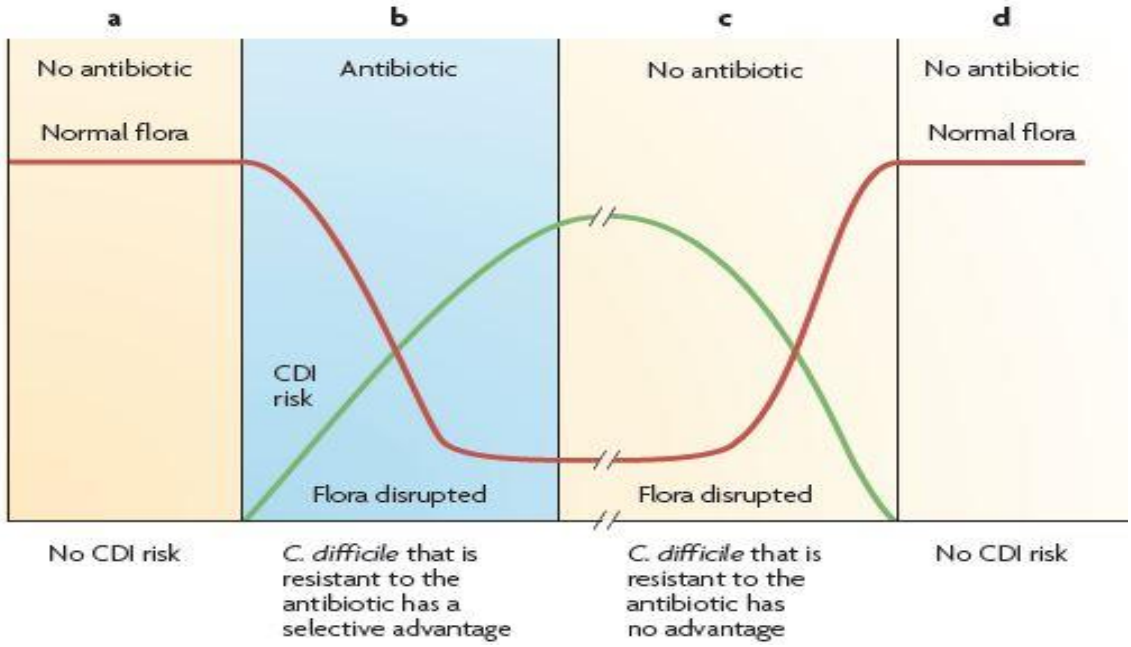


Figure 1.2: The risk of CDI after disturbing normal gut flora caused by an exposure to antibiotics. reproduced with permission (46).

Whilst overall usage of antibiotics has been shown to be related to the increased incidence of CDI, particular classes of antibiotic have been shown to have more impact than others. In a study that was conducted by Pépin *et al.*, the authors found that receiving fluoroquinolones, cephalosporins (first, second or third generations), macrolides, clindamycin or intravenous β-lactam/β-lactamase inhibitors were independent factors associated with CDI (78). However, among those antibiotics, they found that fluoroquinolones and third-generation

cephalosporins were the classes most prone to induce CDI (crude hazard ratio: 5.43 and 4.02, respectively). Results from a recently published systematic review found that the risk of CDI was highest within patients who received third-generation cephalosporins compared to other antibiotics (77).

Due to the adverse impact on clinical outcomes and healthcare cost, strategies and guidelines have been proposed to reduce the incidence and spread of CDI (79-81). For example, the Society for Healthcare Epidemiology of America and the IDSA published clinical practice guidelines to treat and control CDI (82). Two major recommendations with regard to antibiotics were advocated to reduce the risk of CDI:

1- To keep the consumption of antibiotics as low as possible by, for example, minimising the duration and the number of prescribed antibiotics.
2- Implementation of an antimicrobial stewardship program to target the high-risk antibiotic classes, such as fluoroquinolones and third-generation cephalosporins.

These recommendations are supported by studies examining the impact of minimising use of high risk antibiotics and the incidence of CDI (83, 84). In a prospective controlled interrupted time series (ITS) study which was conducted over three years, it was found that CDI incidence rates decreased significantly after an implementation of a policy that led to less use of broad-spectrum antibiotics such as cephalosporins and amoxycillin/clavulanate, and greater use of narrower-spectrum antibiotics, benzylpenicillin, trimethoprim and amoxycillin (85). Similarly, Talpaert *et al.* found that CDI incidence rates significantly decreased after revision of the hospital's local antibiotic prescribing guidelines (86). The revised guidelines encouraged the use of low risk antibiotics and discouraged the use of high-risk antibiotics. This resulted in a significant reduction in fluoroquinolone and cephalosporin usage, which was associated with a consequential reduction in CDI (incidence rate ratio: 0.34; $p < 0.0001$).

1.2.3. Bacterial resistance and antibiotic therapy

In the literature, the term antibiotic resistance (ABR) generally refers to bacterial pathogens that were once susceptible to an antibiotic, but which have since acquired resistance (8). The World Health Organisation (WHO) has raised concerns that if the increasing rates of the ABR are not controlled, we may reach a post-antibiotic era where common infections that have until now been easily treated, may become lethal (8). These concerns are supported by data from a recent WHO report which indicated a dramatic increase in the rates of ABR in common infectious diseases, such as urinary tract infection and pneumonia, both community and hospital-acquired infections (8). Of these resistant bacteria, the most commonly identified resistant pathogens that are associated with poor clinical outcomes are referred to as the "ESKAPE" pathogens (87):

- ***E****nterococcus faecium*
- ***S****taphylococcus aureus*
- ***K****lebsiella pneumoniae*
- ***A****cinetobacter baumanii*
- ***P****seudomonas aeruginosa*
- ***E****nterobacter species*

The rates of ABR for five bacterial pathogens (Staphylococcus aureus, Escherichia coli, Streptococcus pneumoniae, Enterococcus faecalis and Enterococcus faecium) have been investigated in Europe over four years from 2002 to 2006. The report estimated that the overall rate of resistance for these pathogens increased by 6.4% annually (88). Another report from the United States (US) found that the rate of hospitalisation with vancomycin-resistant *Enterococcus faecium* (VRE) has almost tripled from 3.6 to 9.5 cases per 100 000 population over the period 2003 to 2006 (89). A report from the Centers for Diseases Control and

Prevention (CDC) indicated that carbapenem-resistant *Enterobacteriaceae* (CRE) has risen over the last decade, from 1.2% of strains in 2001 to 4.2% in 2011 (90).

The rise in ABR has become a public health concern worldwide due to the impact this has on patients' clinical outcomes and healthcare costs (91-95). With respect to mortality rates associated with ABR, data from the USA estimated almost 23,000 deaths per year due to infections were caused by resistant pathogens (45). Studies indicate that mortality rates among patients who are infected with MRSA are higher than that among those who are infected with methicillin-susceptible *Staphylococcus aureus* (MSSA) (96-99). Other studies that investigated the mortality rates among patients in 1265 ICU from 75 countries, found that the mortality rate for patients with MRSA was almost 9% greater than those who were infected with the MSSA (29.1% vs 20.5%, respectively) (100).An observational study conducted on patients with blood infections caused by *Enterococcus faecium* found that patients who were infected with VRE had higher mortality rates than those who were infected with vancomycin-susceptible pathogens (101).Moreover, patients who are infected with ABR pathogens are more likely to stay longer in hospital (8). Mauldin *et al.* investigated the impact of infections caused antibiotic-resistant Gram negative pathogens on the LOS compared to antibiotic-susceptible Gram-negative pathogens. The authors showed that the LOS increased significantly, by 23.8% for patients with resistant pathogens ($p < 0.001$) (102). In another study, de Kraker *et al.* found that LOS was on average eight days longer among patients with bacteraemia caused by infection with *Escherichia coli* resistant to third-generation cephalosporins, compared to patients with susceptible strains of the same pathogen (103).

The costs of treating infections caused by resistant bacteria are believed to be consistently greater than for infections caused by susceptible pathogens. In their study of 662 hospitalised patients with an infection caused by gram-negative bacteria, Mauldin *et al.*

reported that the estimated direct healthcare costs for patients with resistant pathogens were 29.3% higher than the costs of susceptible pathogens (102). Another study examining the healthcare costs of 725 hospitalised patients with infections caused by *S aureus* found that estimated total healthcare costs for patients with resistant pathogens were more than twice that for those patients with susceptible organisms ($34,657 vs $15,923 respectively; $p < 0.001$) (104). A study looking at 5,699 hospitalised patients found that the total cost was almost $10,000 more when a patient was infected with one of the ESKAPE pathogens (105).

One of the major concerns regarding ABR is that use of antibiotics is now integral to many aspects modern medical practice and without access to reliable antibiotic therapy this may be jeopardised. For example, antibiotics play a major part in cancer treatments, general surgery and organ transplantations (45). In their review article, Smith and Coast stated that losing antibiotic effectiveness to treat common infections would put the era of modern medicine in danger and this would lead us to return to the pre-antibiotic era (106).

A large and growing body of literature has examined the association between antibiotic consumption and increased rate of ABR (29, 107-110). Prior exposure to antibiotics is considered as the major cause of the emergence and rise of ABR. In an investigation on the consumption of antibiotics in the outpatient settings of 26 European countries, it has been shown that ABR rates were higher in countries who consumed more antibiotics (Figure **1.3**) (29).

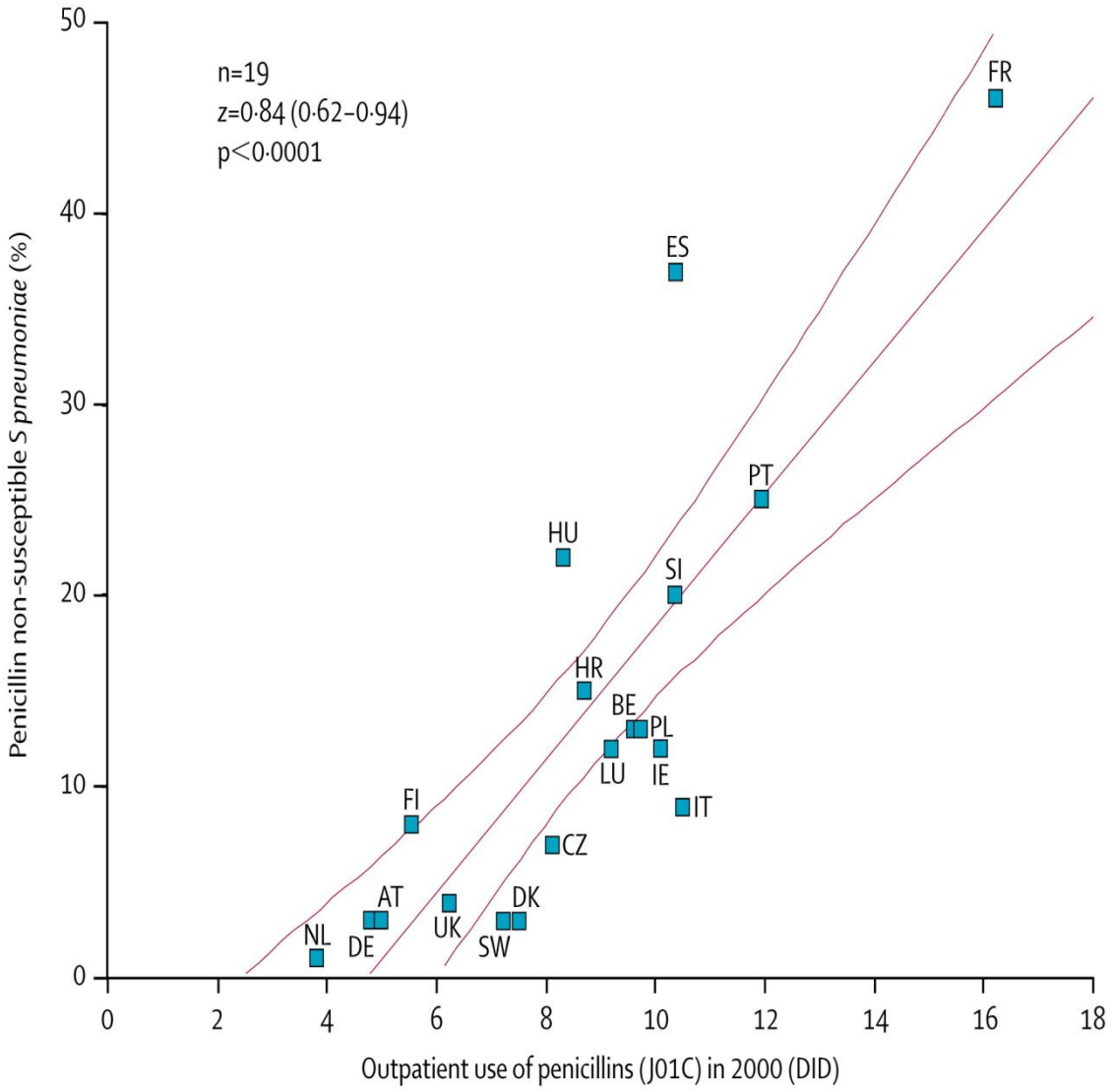


Figure 1.3: Correlation between out-patient penicillin consumption and prevalence of penicillin *S pneumoniae-resistant* incidence among European countries. Reproduced with permission (29).
DID: defined daily dose per 1000 inhabitants daily
AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

Whilst the use of any antibiotic may lead to the emergence of resistance, the use of certain antibiotics may be associated with a particularly significant increase in the rate of some resistant microorganism. For example, Bergman *et al.* conducted a study in which they tested *S. pneumoniae* isolates to indicate the rates of resistance to penicillin and macrolides (111). The data was then compared against the local consumption of macrolides and cephalosporins

in the 18 participating hospitals. The authors found that there was a significant association between increase macrolide usage, azithromycin in particular, and the increase of macrolide-resistant *S pneumonoae*. Furthermore, a connection between increase use of cephalosporins and a rise of *penicillin-resistant S pneumoniae* was indicated. Therefore, the authors highlighted the importance of avoiding unnecessary use of these agents.

Studies have been conducted to examine the effect of controlling broad-spectrum antibiotic use on ABR in some bacterial pathogens. For example, an Australian national restriction on the use of fluoroquinolones in human and animals was associated with reduction of the emergence of resistant E coli (112). Another example comes from Finland, where a decrease in the national consumption of macrolides in the outpatient setting was associated with a significant decrease in the detection of macrolide-resistant group A streptococci (113). It has also been shown that restriction of carbapenem antibiotics was associated with significant reduction of the rate of carbapenem-resistant *Pseudomonas aeroginosa* in 22 US teaching hospitals, where restriction was applied (114). Kaki *et al.* conducted a systematic review on the impact of quality improvement initiatives in critical care units to improve antibiotic prescribing (115). From the 24 analysed studies, 13 evaluated the impact on ABR; where the authors concluded that most of those interventions have been significantly associated with reduce resistance of key ICU pathogens.

Based on the wealth of literature available regarding ABR, four core actions have been proposed in order to tackle the problem (45, 116):

- Preventing the occurrence of infection and the spread of the ABR.
- Tracking resistant microorganisms
- Assisting pharmaceutical industries in developing new antibiotics and new diagnostic tests for resistant bacteria

- Implementing antimicrobial stewardship (AMS)

Although the first three core actions are important strategies, it is beyond the scope of this thesis to discuss these topics in depth and the focus will hereafter be on AMS.

1.3. Antimicrobial stewardship (AMS)

AMS is a relatively new concept that is increasingly gaining popularity in hospital settings (117). AMS is defined as "*an ongoing effort by a health-care institution to optimise antimicrobial use in order to improve patient outcomes, ensure cost-effective therapy and reduce adverse sequelae of antimicrobial use (including antimicrobial resistance)*" (117, 118).

1.3.1. Evidence for AMS

Evidence for the effectiveness of AMS in reducing broad-spectrum antibiotics usage, and improving clinical outcomes is growing (83, 115, 119-126). An Australian study evaluating the impact of AMS at a tertiary care centre reported 10% and 17% reduction in the use of broad-spectrum antibiotic prescribing in the general medical and intensive care unit respectively (120). Additionally, Michael *et al.* conducted a prospective study of ABR and CDI rates three years before and after the implementation of AMS. The study found that the rate of CDI, VRE and MRSA decreased significantly after introduction of AMS to their institution. This was associated with a 9.8% reduction in antibiotic usage and an estimates saving of more than $1.7 million at the end of the three years of the program(127).

A systematic review of interventions aimed at improving antimicrobial prescribing practices highlighted the unique role of AMS in improving clinical outcomes and decreasing the associated healthcare costs (128). In this Cochrane review article, the authors examined the effectiveness of AMS on reducing the incidence of ABR, CDI and clinical outcomes. It was found that AMS initiatives that aimed to minimise the unnecessary and inappropriate prescribing of antibiotics associated with a significant reduction in CDI and ABR incidences,

which was associated with a significant reduction in mortality rate. With regard to the effect of AMS in healthcare costs, the review study analysed ten studies where the healthcare costs were one of the measured outcomes. Eight of the analysed studies indicated a significant saving of money.

1.3.2. AMS and clinical governance

AMS has been proposed as an essential element of the clinical governance framework to improve antimicrobial prescribing within healthcare settings (117). There is an increasing interest from professional and governmental organisations in developing guidelines and recommendations to implement AMS in hospitals (117, 129-133).

AMS is quite high on the agenda of the European Union with 16 European nations developing national strategies to combat ABR and encouraging prudent use of antibiotics (134). One such plan that stands out from others is the Scottish Management of Antimicrobial Resistance Action Plan (ScotMARAP) that was developed by the Scottish government in 2008 (135). ScotMARAP recommends a national framework to implement AMS programs nationally in all acute-care hospitals. The Scottish clinical governance structure to influence the prescribing of antibiotics in a hospital setting is demonstrated in Figure **1.4**. The application of the action plan was associated with a significant reduction in the incidence of CDI in Scotland and improved the management of common infections, such as CAP (136).

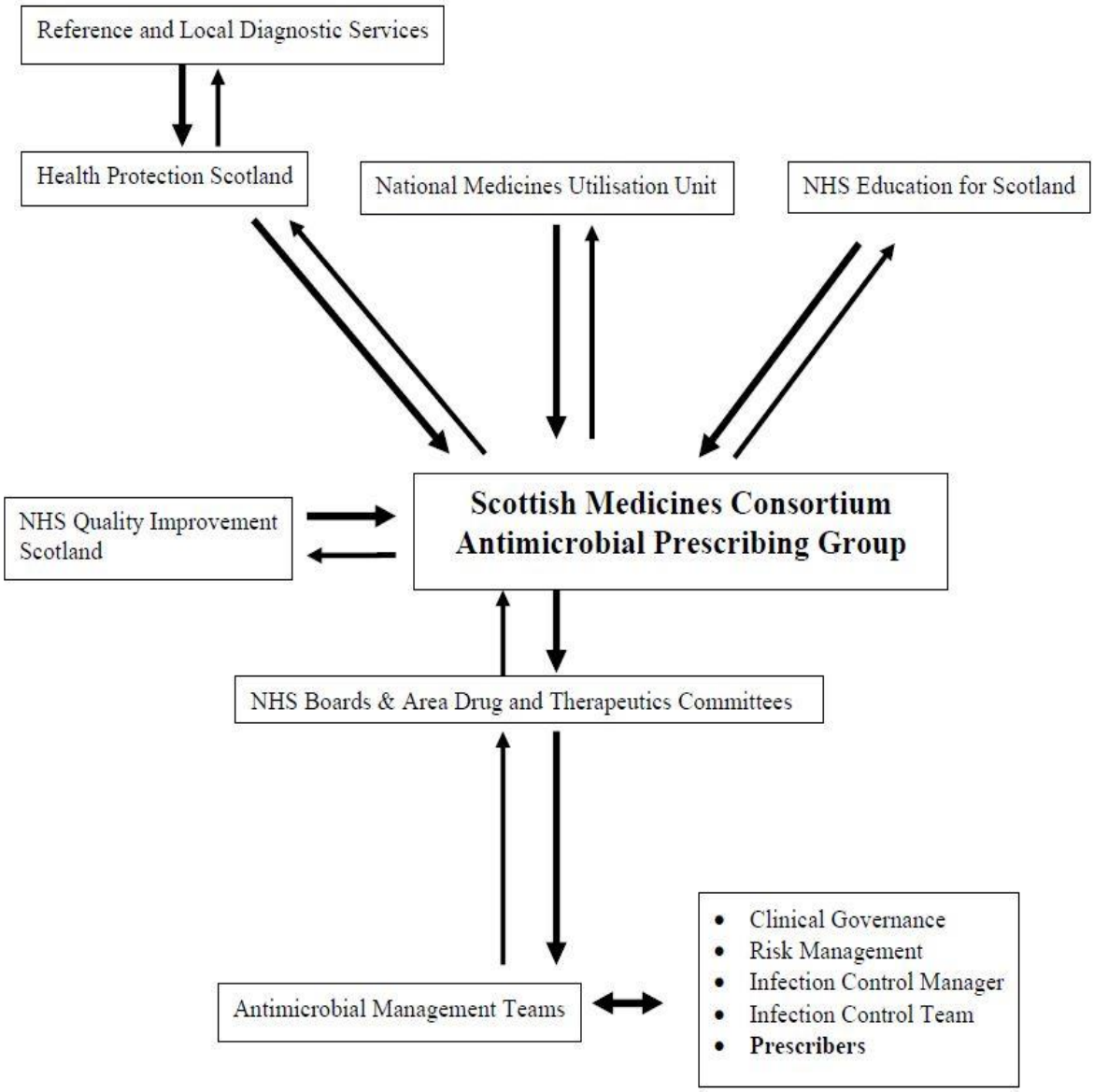


Figure 1.4: The proposed pathway to implement successful AMS, or antimicrobial management team, to influence antibiotic prescribing within acute hospital settings in Scotland. Reproduced with permission.

The Australian Commission on Safety and Quality in Health Care (ACSQHC) established a program in 2007 with the aim of reducing the threat of resistant microorganisms (137). One of the program's elements was the establishment of AMS in Australian hospitals in order to implement effective strategies to ensure appropriate and safe antibiotic usage. In order to facilitate implementation of AMS, ACSQHC published an electronic book, which is available online free, to provide guidance on establishing a successful AMS program among

Australian hospitals (117). The book provides specific examples of successful AMS initiatives in Australia. A 2008 national survey looking at antimicrobial stewardship programs among Australian hospitals found that only 25% of the 80 surveyed hospitals had AMS teams (138). In an investigation into barriers to establishment of AMS programs in Australian hospitals, Chen *et al.* found that lack of education, prescribing habits, inadequate resource and lacking of feedback on antimicrobial prescribing were the common identified obstacles to implementation of AMS program (139). Additionally, the study found that only 17.5% of the respondents who participated in the survey indicated the use of key performance indicators to determine the success of AMS programs; however, indicators were varied among institutions. Chen *et al.* argue that standard national standards to measure the success of AMS programs should be developed to be used as a model (139).

ACSQHC has recently developed quality standards addressing the prudent use of antimicrobials in Australian hospitals. As a part of the accreditation standards, AMS is no longer an optional quality assurance activity in Australian hospitals. Since January 2013, all hospitals in Australia have been required to establish AMS in their institutions in order to gain accreditation against the National Safety and Quality Health Service Standards (140).

Recently, the US government has followed the steps of Australia and European countries in implementing a national action plan to combat the increasing rates of ABR (141). Besides proposed strategies to encourage the development of new antibiotics, the US government has ordered the implementation of a framework to evaluate the government regulations of AMS programs. In short, there has been an increasing governmental recognition of the problem of ABR and its correlations with the misuse of the existent antibiotics. To slow down the existence antibiotics turning ineffective due to ABR, many governments have established national strategies for optimal clinical practice with regard to antibiotic prescribing.

1.3.3. Elements for successful AMS

Several elements of successful AMS have been reported in the literature (142). It has been suggested that an effective AMS program in a hospital setting requires a multidisciplinary team which could include general physicians, pharmacists, infection control professionals, microbiologists, administrators, and infectious disease physicians (117, 129, 143). The main aim of the multidisciplinary team is to develop strategies that aim to enhance antibiotic prescribing among physicians. It is suggested that these strategies are developed by the AMS team and endorsed by an appropriate committee, along with support from hospital executives. ACSQHC considered the following as essential components of a successful AMS program in Australian hospitals (117):

1- Development of local antibiotic prescribing guidelines based on the latest version of the TG, with incorporation of MINDME messages (144):
   - **M**icrobiology guides therapy wherever possible
   - **I**ndications should be evidence-based
   - **N**arrowest spectrum required
   - **D**osage appropriate to the site and type of infection
   - **M**inimise duration of therapy
   - **E**nsure monotherapy in most cases
2- Development of a restricted antibiotic list, including broad-spectrum antibacterial agents and a clear process of how to obtain the required approval.
3- Reviewing antimicrobial prescribing at an individual level and make interventions with direct feedback to the prescriber.
4- Monitoring the overall prescribing practice for antibiotics, such as the use of broad-spectrum antibiotics, or the prescribing habits for a common infection.

5- Ensure that the implemented antimicrobial guidelines reflect the findings from the hospital's microbiology susceptibility reports.

Other strategies have been found to effectively change antibiotic prescribing behaviour, such as education targeting healthcare professionals about the best use of antibiotics (145-147), the use of a computerised decision support system (119, 122, 148, 149), routine AMS rounds (120), and the use of a web-based antimicrobial approval system (120).

Among Australian hospitals, several strategies have been utilised by AMS teams to improve antibiotic prescribing and reported as successful in published studies. A snapshot of AMS activities across Australian hospitals found that multifaceted initiatives were used in order to optimise the use of antibiotics. The initiatives that were commonly reported as being used and perceived as moderately to extremely successful by most respondents include (138):

- Obtaining approval from the Drug and Therapeutic committee or equivalent for the antibiotic list and their use
- Having a restricted policy regarding antibiotic prescribing
- Developing locally antibiotic policies
- Involvement of a pharmacist and an infectious disease physician in the AMS activities
- De-escalation or streamlining antibiotic prescribing based on microbiology results
- Utilisation of clinical guidelines and pathways

1.4. Behavioural change in clinical practice

A considerable amount of literature has been published showing that the research evidence frequently fails to be reliably incorporated into routine clinical practice in a timely way (150-152). In the case of antibiotic prescribing, for example, studies indicate that almost

half of all use is considered unnecessary or inappropriate (117). Accordingly, efforts have been made to implement evidence-based medicine in daily clinical practice relating to the treatment of infection.

The impact of different strategies on modifying prescribing behaviour has been studied by several researchers (128, 153, 154). One of the most commonly used strategies was the development and dissemination of evidenced-based guidelines. However, to date there has been little agreement on the best approach to increase adoption of the recommendations in these guidelines (155). Therefore, it has been suggested that strategies to change clinical practice should be tailored to address the different barriers that may impede adoption of the desired recommendations (155). It has been shown that a multifaceted intervention based on these known barriers is more likely to lead to change (153).

In general, a variety of barriers may hinder doctors from adhering to clinical practice guidelines. These barriers include three main themes: knowledge, attitude and behaviour as shown in Figure 1.5 (151). In terms of antibiotic prescribing, several qualitative and quantitative studies have investigated potential barriers that hinder doctors from adhering to recommended antibiotic guidelines (156-164). For example, in their recent survey of barriers to appropriate prescribing of antibiotics in three Australian tertiary teaching hospitals, Chaves *et al.* identified three barriers; a lack of antibiotic prescribing knowledge among junior doctors, lack of awareness about the restricted list of antibiotics, and a reliance on senior doctors to prescribe antibiotic (165). However, barriers to appropriate antibiotic prescribing might vary between countries, hospitals and even between different medical departments among the same hospital (166). Therefore, it is imperative to identify barriers that affect appropriate prescribing of antibiotics in an institution where an intervention would take place.

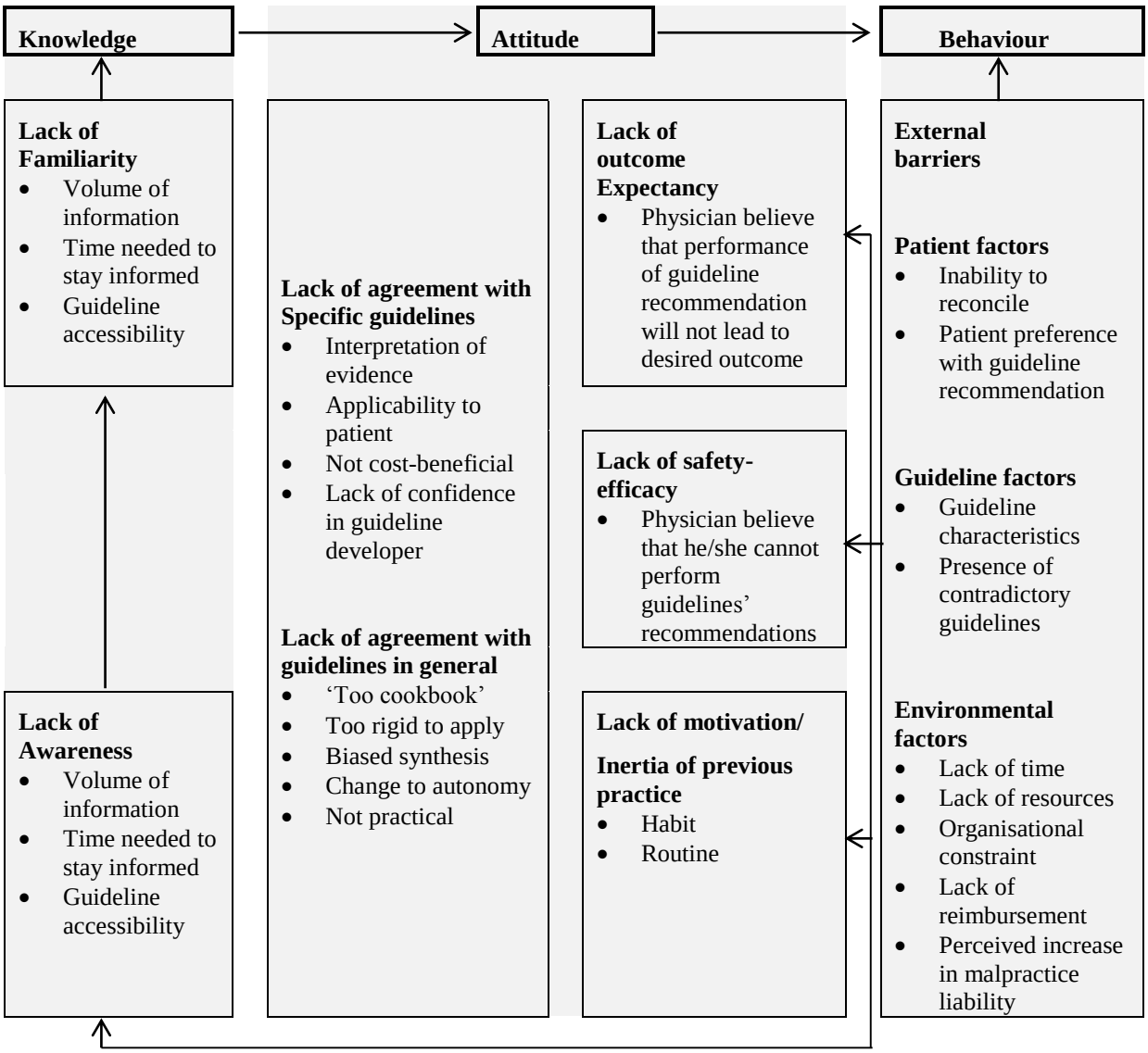


Figure 1.5: Barriers that could hinder doctors from adhering to clinical practice guidelines. Adapted and reproduced with permission (151).

1.5. AMS and disease-specific clinical practice guidelines

Inappropriate use of antibiotics, particularly those with broad-spectrum antibacterial coverage, is frequent among common infections (167, 168). It was estimated that almost 4 out of 10 patients received antibiotic regimens that were deviated from recommended antibiotic guidelines among hospitals (172). Therefore, it seems reasonable to target those infections for quality improvement initiatives.

It has been recommended that implementation of clinical guidelines for the management of common infections and surgical prophylaxis is a high priority when seeking to improve antibiotic use (133, 157). A number of studies have examined impacts of implementation of disease-specific clinical practice guidelines (169, 170). Most of these interventions targeted antibiotic prescribing for surgical prophylaxis and empirical therapy for the management of skin and soft-tissue infections (SSTI), urinary tract infections (UTI), sepsis and lower respiratory tract infections (LRTI) (171-176). Table **1.1** provides some examples regarding the impacts of AMS initiatives for the management of these common infections on antibiotic prescribing performance and patients' clinical outcomes.

Table 1.1: Examples of the impact of AMS initiatives to improve the management of common infections on the prescribing performance and patients' clinical outcomes.

Site of infection	AMS initiative	Outcomes
Surgical prophylaxis (177)	Implementation of an optimised and restrictive antibiotic prophylaxis policy based on national guidelines.	The intervention resulted in Reduction in antibiotic use for surgical prophylaxis by 35%. Overall decrease of SSI from 5.4% to 4.5% ($p = 0.22$); significant.
SSTI (171)	Implementation of clinical practise guidelines for the management of SSTI. The guideline was actively implemented by using three main strategies: educational campaign, electronic admission order set and auditing and feedback of the prescribing practice.	The intervention resulted in less use of antibiotics with broad gram negative coverage (66% vs 36%; $p < 0.001$) and broad anaerobic coverage (76% vs 49%; $p < 0.05$). Additionally, the intervention resulted in a shorter median duration of antibiotic administration (13 days vs 10 days; $p < 0.01$).
UTI (178)	Implementation of electronic UTI order set followed by audit and feedback to improve the empirical antibiotic management for patients with uncomplicated UTI who presented in the ED.	The AMS intervention was associated with an increase of the compliance with the clinical guidelines by 38% (44% vs 82%; $p < 0.05$) and a decrease use of broad-spectrum antibiotics, fluoroquinolones, by 31% (44% vs 13%; $p < 0.001$).
Sepsis (179)	Implementation of a first-dose stat antibiotic policy to deliver appropriate antibiotics within 15 minutes to patients who were diagnosed with sepsis.	The mean ICU LOS significantly decreased after the implementation of the policy (5.9 days vs 4.2 days; $p < 0.01$). Moreover, the intervention was associated with a significant reduction in cost per case ($14,378 vs $12,311; $p < 0.05$).
LRTI; hospital acquired pneumonia (HAP) (180)	Implementation of local hospital guidelines for the management of HAP.	The intervention led to significant increase in appropriate antibiotic prescribing (34% vs 62%; $p < 0.01$).
LRTI; community acquired pneumonia (CAP) (181)	Implementation of CAP clinical practice guidelines in the emergency department.	The intervention led to a 35.1% increase in the administration of appropriate antibiotic regimens (60.4% vs 95.5%, $p < 0.001$) and a 17% reduction in hospital admission (36.5% vs 19.5%; $p < 0.001$). In terms of clinical outcomes, mean LOS reduced by 1.1 day ($p < 0.05$), and re-admission within 30 days was less by 24.1% after the intervention (28.6% vs 4.5%; $p < 0.05$).

This thesis intends to examine and evaluate the impact of an intervention to improve the adherence to the CAP guidelines on antibiotic prescribing and patients' clinical outcomes. Thus, this topic will be discussed in a greater length in the next section.

1.6. Community-acquired pneumonia (CAP)

1.6.1. Definitions

Community Acquired Pneumonia (CAP) has been defined as an infection that occurs at the lung parenchyma, and for which the onset occurs outside of hospital or within 48 hours of hospital admission (144). However, different guidelines use different criteria to define CAP. For example, the guidelines of the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) differentiate between patients who live in the community and those who are residents of nursing homes (NH) or long care facilities, referring to the former as CAP and to the latter as nursing and health-care associated pneumonia (NHCAP) (182, 183). It has been found that elderly patients (65 years and older) with CAP are more likely to be infected with ABR pathogens as NH residents (10.2%) compared to patients who are admitted from a community-based setting (2.7%) (184). With respect to clinical outcomes, one study suggested that the mortality rate is higher within NH residents (14.1%) then within non-NH residents (4.6%) (184). However, despite these possible differences, TG14 makes no differentiation between community-dwelling and NH patients when it comes to treatment recommendations (144).

1.6.2. Diagnosis

Clinical symptoms for patients with suspected lower respiratory tract infections include acute pulmonary symptoms (such as cough, sputum production, and chest pain), with or without fever. Other symptoms may be present such as headache and diarrhoea, and among the elderly, features present might not be specific (144). For example, it is less likely that patients aged 80 years or older would be present with chest pain, headache or fever (185).

Relying on physical examination to diagnose CAP can lead to misdiagnosis. Therefore, performing chest radiography is recommended in many guidelines for those patients who present themselves in the emergency department (ED) with a suspected diagnosis of CAP. The presence of any new or worsening chest radiological changes (such as an infiltrate) may help confirm the diagnosis of CAP and rule out other lower respiratory tract infections such as infective exacerbation of chronic obstructive pulmonary disease (IECOPD) (144, 182, 186).

1.6.3. Incidence

The incidence of CAP varies between regions. In South America, the incidence of patients treated for CAP as out-patients ranges from 335.8 to 804.9 per 100,000 inhabitants per year (187). In the US, the estimated incidence of CAP within the age group 18-64 is 489 per 100,000 inhabitants per year (188). In European countries, the annual incidence rate of CAP ranges from 154 to 170 per 100,000 of the population (189). In Australia, the overall annual incidence of CAP data is lacking. However, the estimated number of pneumonia consultations at general practitioners is 343,000 per year (190).

1.6.4. Hospitalisation

CAP represents one of the most frequent conditions that require hospitalisation. It was estimated that around 100,000 patients with CAP were hospitalised in Australian hospitals in 2003/2004 (191). In the US, more than four million visits to hospital clinics were due to pneumonia in 2006, and from those almost 600,000 patients were hospitalised (192, 193), while up to 680,000 people in Germany are admitted to hospitals with CAP each year (194).

1.6.5. Length of hospital stay (LOS)

In Europe, the mean LOS for patients admitted to hospital due to CAP is estimated to be 6 days (range: 2.2 – 9.8 days) (194-196). Several factors might contribute in delaying hospital discharge for patients admitted with CAP. These factors include advanced age, severe CAP, change

in mental status, co-existing cardiopulmonary diseases, diabetes mellitus, ICU admission and multi-lobar pneumonia (195). Besides patient characteristics, inappropriate antibiotic prescribing has also been identified as an independent risk factor for long hospital stay (197).

1.6.6. Mortality

CAP is a major cause of mortality in Australia and worldwide. Pneumonia, alongside influenza, was responsible for 2% of all deaths in Australia in 2006, and the overall 30-day mortality rate for hospitalised patients with CAP was estimated to be 5.6% (198). Additionally, it is the 8th leading cause of death in the US (199). Inpatient mortality rates for patients with CAP ranged from 10% to 35% in South America (age ≥ 50) (187). In European countries, the mortality rates due to CAP varied widely from less than 1% to 48% of CAP patients (200).

Several factors might contribute to the rise in mortality rates. First, mortality rate is dramatically increased with age (187, 200, 201). Patients aged less than 65 are more likely to present themselves with mild CAP, and their mortality rate is less than that among patients of an older age (1.7% vs 8.2%). The short- and long-term mortality rates were shown to be significantly lower among those of a young age (202). Moreover, mortality rate increases with severity, which ranges from less than 1% for mild CAP to 27% for patients with severe CAP (203). Pre-existing diseases could also play an important factor. For example, patients with COPD have a higher mortality rate than those without such a disease (204). However, another study has shown no significant differences between the two groups (205).

1.6.7. Healthcare costs

Globally, CAP has had a significant economic impact on the healthcare system. In European countries, around €10.1 billion are estimated to be spent annually on treating CAP, with a direct cost of €6.4 billion for inpatient care, outpatient care, and medications. The indirect costs of €3.6 billion are due to lost work days as a result of the disease (200). In the US, the estimated direct and

indirect cost for population aged 18-64 is $10.6 billion per year. Of these, 80% are due to direct health care costs, and the rest (20%) comprise the costs of lost work days (188). Moreover, the estimated direct cost among the elderly (≥ 65 years old) is $7.3 billion per year (206), and the main factor that contributes to the increasing cost is LOS (207). In Australia, it is estimated that 20 million Australian dollars are spent each year only on visits to the general practitioner due to CAP. The costs include consultations, chest X-ray, and medications (190). However, information regarding the healthcare cost of hospitalised patients in Australia is lacking. According to Lave *et al.*., it is estimated that hospitalisation due to CAP accounted for almost 92% of the overall cost, while outpatient treatment only accounted for 8% (208).

1.6.8. Responsible pathogens

Although many pathogens can cause CAP, only a limited number are responsible for most of the cases. *Streptococcus pneumoniae* is the most commonly identified pathogen in patients with CAP (209, 210). In one Australian prospective study that was conducted in 885 patients, it was found that of 348 patients where the causative bacterial pathogens were identified, *Streptococcus pneumoniae* was responsible for almost one-third of the CAP cases (35.3%), followed by *Mycoplasma pneumonia* (22.4%) (Table **1.2**) (210). Although bacteria remain the leading cause of CAP, viruses are frequently identified in patients with CAP (210, 211). However, several factors may alter the pathogen distribution. These factors include patients' residence (NH vs community), severity of the disease, age, comorbidities, and prior antibiotic usage.

Table 1.2: Bacterial aetiology of CAP among Australian hospitals (210).

Identified pathogen	Percentage
Streptococcus pneumoniae	35.3%
Mycoplasma pneumoniae	22.4%
Haemophilus influenzae	12.9%
Legionella species	8.6%
Chlamydophila species	4.3%
Pseudomonas aeruginosa	4%
Gram-negative enteric bacilli	3.7%
Staphylococcus aureus	3.2%
Moraxella catarrhalis	2%
Others	3.6%

The first factor to consider is patients' area of residence. For example, while *Streptococcus pneumoniae* is the leading cause of pneumonia that develops outside hospital, one Japanese study suggested it remains as the second leading cause after *Staphylococcus aureus* for patients who live in NH (212). These resistant strains of the latter *Staphylococcus aureus* are seen more within NH populations, and are associated with a high severity of CAP (213). However, Australian data regarding the bacterial aetiology for patients residing in NH is lacking.

Severity is another factor that should be considered since most guidelines based their empirical management on the severity of CAP (144, 182, 186). In Australia, *Mycoplasma pneumoniae* is the most frequently identified pathogen in mild cases, which is more common in people who are less than 50 years of age (210). Although *Streptococcus pneumoniae* is the most frequently identified pathogen in severe CAP, other organisms such as *Legionella species* and *Pseudomonas species* are seen commonly in such cases (210).

Age plays an important role as well. Although *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* are the most frequently identified pathogens in all age groups (202, 210, 214), the latter

is predominant in younger patients (aged < 65) (210, 214). Furthermore, gram negative bacilli have rarely been seen in those young populations (202).

It has also been found that pre-existing respiratory diseases could increase the risk for specific microorganisms but the results are contradictory. For example, gram-negative bacteria such as *Pseudomonas spp*. are more likely to be identified in patients with IECOPD (210). However, other studies have shown no correlation between the presence or absence of COPD in the case of microbiological profile (214).

Prior antibiotics usage could also help predict the responsible pathogens. In one large cohort Spanish study, it was found that the rate of identified *Legionella pneumophila* was three times higher for patients with CAP who had received antibiotics before admission to the hospital than those who had not (215). The same study found, on the other hand, that *Streptococcus pneumoniae* was less likely to be identified in this group of patients.

Therefore, taking the patient's medical history can provide a clue as to the possible microorganism responsible for CAP. Table **1.3** describes the specific risk factors, in an international context, associated with microbial aetiology of CAP according to IDSA/ATS. Some of these may be less relevant in Australia.

Table 1.3: Risk factors and most commonly identified bacterial pathogens (182)

Condition	Commonly identified pathogens
Alcoholism	*Streptococcus pneumoniae, oral anaerobes, Klebsiella pneumoniae, Acinetobacter species, Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella species, Streptococcus pneumonia, Moraxella catarrhalis, Chlamydophila pneumoniae*
Aspiration	*Gram-negative enteric pathogens, oral anaerobes*
Lung abscess	*community acquired methicillin resistant staphylococcus aureus, oral anaerobe, endemic fungal pneumonia, Mycobacterium tuberculosis, atypical mycobacteria*
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetti*
Human Immunodeficiency Virus (early)	*Streptococcus pneumoniae, Haemophilus influenza, Mycobacterium tuberculosis*
Human Immunodeficiency Virus (late)	*Streptococcus pneumoniae, Haemophilus influenza, Mycobacterium tuberculosis, Pneumocystis jirovecii, Cryptococcus,, Aspergillus, atypical mycobacteria, Pseudomonas aeruginosa, Haemophilus influenzae*
Hotel or cruise ship stay in the previous two weeks	*Legionella species*
Influenza active in community	*Streptococcus pneumonia, staphylococcus aureus, Haemophilus influenzae*
Cough more than two weeks with whoops or post-tussive vomiting	*Bordertella pertussis*
Structural lung diseases	*Pseudomonas aeruginosa, Burkholderia cepacia, staphylococcus aureus*
Injection drug use	*staphylococcus aureus, anaerobes, Mycobacterium tuberculosis, Streptococcus pneumoniae*
Endobronchial obstruction	*Anaerobes, Streptococcus pneumonia, Haemophilus influenza, staphylococcus aureus*

1.6.9. Antibiotic-resistant *Streptococcus pneumoniae*

The emergence of ABR has become a challenge and caused great problems for the management of CAP (216). One of the determining factors for the empirical management of CAP recommendations in various practice guidelines is antibiotic resistance to *Streptococcus pneumoniae*. The rate of antibiotic resistance to *Streptococcus pneumoniae* could vary from region to region, country to country, and even between states within the same country. This is why hospitals are encouraged to develop a local guideline for the management of CAP based on the national guidelines, taking into account the resistance rate of *Streptococcus pneumoniae* toward common antibiotic groups such as penicillins, macrolides, tetracyclines, and respiratory floroquinolones (117, 182, 186).

The minimum inhibitory concentration (MIC) of penicillin toward *Streptococcus pneumoniae* has been changed since 2008 for non-meningeal infections (217) (Table **1.4**). By this new definition, many isolated *Streptococcus pneumoniae* that were considered resistant bacteria would be defined as susceptible pathogens after 1st of January 2008, such that all publications before 2008 should be interpreted with caution For instance, in one Australian prospective study that was conducted in the period 2004-2006, it found that around 7.3% of the isolated *Streptococcus pneumoniae* from CAP patients were considered to be intermediate resistance (MIC; 012-1 μg/ml) while only one isolate was considered a resistant pathogen (MIC; 2 μg/ml) (210). Under the new break point, all those isolates would be susceptible to penicillins. Therefore, penicillins, coupled with a good coverage of *Streptococcus pneumoniae*, is recommended as a first line therapy for patients with mild CAP as per TG14 (144).

Table 1.4: Break points to identify non-meningeal *Streptococcus pneumoniae's* susceptibility toward penicillins.

Period	MIC (µg/ml) by susceptibility category		
	Susceptible	**Intermediate**	**Resistance**
Before 1st January 2008	≤ 0.06	0.12 - 1	≥ 2
After 1st January 2008	≤ 2	4	≥ 8

The incidence of macrolide-resistant *Streptococcus pneumoniae* varies among countries and can be as low as 1% and as high as 50% in different European countries (218). In Australia, there is an increasing trend of macrolide-resistant *Streptococcus pneumoniae*. From 1994 to 2005, the macrolides' resistance increased threefold in Australia (from 8% to 22%) (219). Therefore, a macrolide monotherapy regimen is only recommended by TG14 as an alternative therapy in the case of penicillin allergy or when an atypical pathogen is suspected to be the cause of diseases (144). Furthermore, the ATS/IDSA CAP guidelines only recommend the use of monotherapy macrolides as a first line therapy for mild CAP among patients who had been previously healthy and had not used any antibiotic within the last three months (182).

Tetracycline (doxycycline in particular) is one of the most commonly prescribed antibiotics for the management of CAP (220). However, it is only recommended to be used alternatively as a monotherapy for patients with mild CAP (144). The resistance of tetracycline has been found to be as high as 18.4% in Australia according to 2005 data (219).

1.6.10. CAP severity and scoring system

To improve the care of patients with CAP, a number of different scoring systems have been developed to help assess its severity. These scoring system has been subsequently utilised to guide the appropriate antibiotic therapy in terms of drug selection, route and whether management should be in the out-patient or in-patient (including ICU) settings (144, 182, 186). Several severity scoring systems have been developed, with the most known being the Pneumonia severity index (PSI) and

CURB65. SMART-COP and CORB are advocated by TG14 (144). However, there is no agreement amongst physicians on the best scoring tool to use (221). Despite the recommendation to use a scoring system to assess the need for hospital admission, several factors should be taken into account. These factors include co-existing diseases, the presence of pleural effusion, complications from pneumonia, reduced compliance and social factors (222).

Mortality predictors' severity tools

Both PSI and CURB65 severity tools are based on the 30-day mortality rate (Table **1.5**) (223, 224). The mortality rate increases with increased scoring (225). While the PSI is better at identifying patients with low mortality risk, the CURB65 could predict patients at high risk more accurately (226). However, several studies show that CURB65 is as effective as PSI in predicting mortality (227, 228).

Table 1.5: Prediction of the mortality rates based on PSI and CURB65 values.

PSI mortality rates by classes	**Predicted mortality rate**
I - II	1.1%
II (≤ 70)	0.7%
III (71-90)	2.8%
IV (91-130)	8.5%
V (> 130)	31.1%
CURB65 mortality rates by scores	**Predicted mortality rate**
0 -1	1.5%
2	9.2%
3 or more	22%

The British Thoracic Society (BTS) and IDSA/ATS CAP guidelines prefer to use the CURB65 tool to assess the severity of CAP. This is because it is easier to remember and calculate than PSI. The CURB65 index is simple and less complicated than that seen in the PSI index, which contains 20 variables that include several laboratory variables. On the other hand, CURB65

contains only 5 variables that need to be measured, and it is suitable for busy departments such as ED (182, 186).

PSI scoring system was identified by Fine *et al.* in the US in 1997 (223). The main aim of PSI was to identify the patients with CAP at low risk of death based on the prediction of 30-day mortality rate. This was meant to allow the physician to make an appropriate decision on whether the patient should be treated in or out of hospital (182, 223). The PSI consists of five classes, starting with class I which represents the lowest risk of death (Table **1.6**). The class I and II patient can be treated as an outpatient with oral antibiotics. Class V indicates the highset severity level wherein the patient needs to be hospitalised and ICU care should be considered. To determine the severity score, there are 20 variables such as demographic factors, co-existing disease, physical examination, laboratory and chest X-ray findings that need to be assessed. However, if the patient is under the age of 50, has no comorbidities, and has a normal physical examination, there will be no need to do laboratory tests and the patient will be classified as level I severity and should thus be treated as an outpatient with oral antibiotics. PSI has a low false negative rate which means that it is more sensitive for the identification of patients who have non-severe CAP (229). This can then give the physician more confidence in deciding if the patient needs to be hospitalised or not, especially for those patients who prefer not to be admitted (230). However, due to the high value that the PSI places on age and comorbidities, patients could be categorised into a high risk class even when the risk is actually quite low (231).

Table 1.6: PSI scoring system to identify patients with mild, moderate and severe CAP.

Patient's characteristics	Points
Demographic factors	
Age (male)	Years
Age (Female)	Years – 10
Nursing home resident	10
Co- existing disease	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination findings	
Altered mental status	20
Respiratory rate ≥ 30 breaths/minute	20
Systolic blood pressure < 90 mm Hg	20
Temperature < 35 ˚C or ≥ 40 ˚C	15
Heart rate ≥ 125 beats/minute	10
Laboratory and chest X-ray findings	
Arterial pH < 7.35	30
Blood urea nitrogen ≥ 11 mmol/liter	20
Glucose ≥ 14 mmol/liter	10
Haematocrit < 30%	10
Partial pressure of arterial oxygen < 60 mm Hg	10
Pleural effusion	10

Mild CAP (≤ 70 points), moderate CAP (71 – 130 points), severe CAP (> 130 points)

CURB65 scoring system was designed in the UK by Lim *et al.* in 2003 (224). The aim of CURB65 was mainly to identify people at high risk of death (Table **1.7**). It is based on 5 variables for detecting the severity of the disease: **C**onfusion, **U**rea level (> 7 mmol/l), **R**espiratory rate (> 30 breath per minute), **B**lood pressure (systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg), and aged **65** years or older. CURB65 can divide patients into three groups according to the risk of 30-day mortality: low risk (score of 0-1) who might be treated as outpatients;

intermediate risk (score of 2) who should be hospitalised; and high risk (score of ≥ 3) of mortality who need to be hospitalised with consideration of ICU admission (182, 186, 224).

Table 1.7: CURB65 scoring system to identify patients with mild, moderate and severe CAP.

Patient's characteristics	**Points**
Confusion	1
Urea > 7 mmol/liter	1
Respiratory rate ≥ 30 breaths/minute	1
Blood pressure (Systolic blood pressure < 90 mm Hg or Diastolic blood pressure ≤ 60 mm Hg	1
Age ≥ **65**	1

Mild CAP (0 – 1 points), moderate CAP (2 points), severe CAP (≥3 points)

Although both PSI and CURB65 have a good prediction rate for risk of mortality, they are not so good when it comes to identifying persons who are most likely to benefit from ICU admission (232). Because of their being heavily influenced by age, both scoring tools were found to be nonspecific and the patient's severity could be overestimated (231, 233).

Predictors of the need for Intensive Respiratory Support or Vasopressor Support (IRVS)

SMART-COP and CORB are the scoring tools which are currently recommended to be used as per TG14 (Figure **1.6**) (144) . Unlike PSI and CURB65, which are based on the prediction of 30-day mortality rate to measure the severity, the SMART-COP/CORB scoring tools, which originated in Australia, aim to measure the severity of CAP according to the need for intensive respiratory support or vasopressor support (IRVS) and ICU admission (234, 235). This is supported by a meta-analysis study which showed that SMART-COP provides better prediction as to the need of ICU than PSI and CURB65 (236). Unlike PSI and CURB65 tools, age has little effect on both SMART-COP and CORB tools. Therefore, the probability of catching severe cases in younger patients is greater when the SMART-COP or CORB tool is used (234, 235).

CORB		SMART-COP	
Variables	Points	Variables	Points
Confusion	1	Systolic BP < 90 mm Hg	2
O_2 saturation ≤ 90%	1	Multilobar CXR involvement	1
Respiratory rate ≥ 30 br/min	1	Albumin < 35 g/l	1
Blood pressure Systolic BP < 90 mm Hg or Diastolic BP ≤ 60 mm Hg	1	Respiratory rate ≥ 30 br/min	1
		Tachycardia ≥ 125 bpm *	1
		Confusion (acute)	1
		Oxygen low * PaO_2 < 60 mm Hg, or O_2 saturation ≤ 90%, or PaO_2/FiO_2 < 250	2
		PH < 7.35	2

Moderate CAP	Severe CAP
(SMART-COP score < 5 and CORB score < 2	(SMART-COP score ≥ 5 or CORB score ≥ 2)

Br/min = breaths per minute, BP = blood pressure, O_2= oxygen, PaO_2 = partial pressure of oxygenation, CXR = chest X-ray, bpm = beats per minute, FiO_2 = fraction of oxygen in inspired air.
*For patients ≤ 50 years old, the value of tachycardia is ≥ 130; and the oxygenation values are PaO_2 < 70 mm Hg, O_2 saturation ≤ 93 and PaO_2/FiO_2 < 333.

Figure 1.6: Identifying the severity of CAP based on CORB and SMART-COP.

The CORB severity tool is aimed at providing a simple tool that can help clinicians decide if the patient requires early aggressive management for CAP or not. CORB contains four easily assessed variables and no invasive testing is needed, which makes it a good tool for clinics and hospitals that may have few facilities. Patients are classified as having severe CAP when two or more of the CORB variables are detected (235).

The SMART-COP severity tool is aimed at identifying the severity of CAP according to the need of IRVS as well as CORB. SMART-COP, compared with PSI and CURB65, is better able to predict patients who need ICU admission and IRVS, and thus facilitates for the right decision to be made early in the ED. Charles *et al.*. found that patients in classes VI and V with PSI or in group three with CURB65 were less likely to receive IRVS when compared to patients who scored three

or more using the SMART-COP scoring tool (234). Patients are classified as having severe CAP when they score 5 points or more (234).

1.6.11. Empirical therapy and CAP guidelines

Since there is no rapid diagnostic method to indicate which pathogens are responsible for the CAP, empirical therapy is commonly used. A patient's clinical presentation is not enough for predicting specific causative pathogens responsible for CAP. The guidelines for empiric antimicrobial therapy are based on providing cover against pathogens most likely to be responsible for the disease (237). Based on the pathogens detected in one multi-centre study in Australia, the recommended antibiotic regimens (penicillin + doxycycline or macrolide) to cover both *Streptococcus pneumoniae* and atypical pathogens were considered adequate for 94.6% of patients with CAP (210). To improve the care of patients with CAP, many countries such as the US, UK and Australia have developed guidelines for the management of the disease (144, 182, 186).

Those guidelines classify patients according to severity (mild, moderate or severe) and site of care (outpatient, inpatient or ICU), and the antibiotics regimen is accordingly recommended. Table **1.8** shows the recommended antibiotic regimens in IDSA/ATS, BTS and TG14 based on the severity and site of care.

Table 1.8: First-line therapy recommendations for CAP in adults as per IDSA/ATS, BTS and TG14 (144, 182, 186).

Setting and severity	IDSA/ATS (2007)	BTS (2009)	TG14 (2010)
Mild CAP/ out-patient	• Macrolide (azithromycin, clarithromycin, or erythromycin) [a] • Fluoroquinolone (moxifloxacin, levofloxacin, or gemifloxacin) • β-lactam (amoxycillin, amoxycillin/clavulanate, ceftriaxone, cefpodoxime, or cefuroxime) + macrolide (Azithromycin, clarithromycin, or erythromycin)	• Amoxycillin	• Amoxycillin
Moderate CAP/ In-patient (non-ICU)	• Fluoroquinolone (moxifloxacin, levofloxacin, or gemifloxacin) • B-lactam (ampicillin, cefotaxime, or ceftriaxone or ertapenem) + macrolide (Azithromycin, clarithromycin, or erythromycin)	• β-lactam (amoxycillin, or benzylpenicillin) + clarithromycin	• Benzylpenicillin + doxycycline or clarithromycin
Severe CAP/ICU	• B-lactam (ampicillin/sulbactam, cefotaxime, or ceftriaxone) + azithromycin or fluoroquinolone (moxifloxacin, levofloxacin, or gemifloxacin)	• Amoxycillin/clavulanate + clarithromycin	• Ceftriaxone, cefotaxime, or (benzylpenicillin + gentamicin) + azithromycin

[a] In the case of absence of co-existing diseases and no antibiotic used in the previous 3 months

Although there is an agreement to empirically cover *Streptococcus pneumoniae* in all guidelines since it is the most likely cause of CAP, covering atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila)* for patients with mild CAP (or who are treated as outpatients) remains controversial (144, 182, 186). For example, the US guidelines recommend a regimen providing atypical cover, such as azithromycin as a first line

therapy or doxycycline as an alternative for the management of patients with mild CAP and without any risk factor of drug-resistant *Streptococcus pneumoniae* (182). Other guidelines, such as the BTS guidelines and Australian TG, recommend amoxycillin as a first line therapy, as the priority is to cover *Streptococcus pneumoniae (144, 186).* Doxycycline or clarithromycin is suggested only as an alternative to extending cover to atypical pathogens if they are suspected.

Although macrolides cover *Streptococcus pneumoniae* and atypical pathogens, several reasons might lead to discouraging routinely prescribing for patients with mild CAP. Firstly, there are no differences with regard to clinical outcome between patients receiving antibiotics that only cover *Streptococcus pneumoniae* and those receiving extended spectrum antibiotics that cover atypical pneumonia (238). Secondly, macrolide resistance to *Streptococcus pneumoniae* is high in some regions such as Europe (239). Therefore, the use of macrolides is not recommended in those regions. Another reason is the relationship between the high usage of macrolides and tetracycline in mild cases and the emergence of *Streptococcus pneumoniae*, which is the main causative organism in CAP (240).

For moderate CAP, guidelines recommend covering *Streptococcus pneumoniae* and atypical pathogens (144, 182, 186). However, there is still controversy regarding a regimen that provides cover against atypical pathogens in moderate CAP. While there are studies that showed the benefit of using macrolides in CAP patients (241), other studies have shown that receiving antibiotics that cover atypical pathogens does not affect mortality rate or success of treatment (242).

A broad-spectrum antibiotic for the treatment of severe CAP is warranted to cover *Streptococcus pneumoniae*, atypical pathogens, and *Enterobacteriaceae spp*. (144, 182, 186). As such, a combination therapy is often recommended to provide additional cover for the atypical pathogens that are commonly identified in severe CAP patients (210), as it has been shown to reduce mortality (243).

1.6.12. Pattern of empirical antibiotic usage

The main reason for choosing one antibiotic regimen over another is to cover the most likely pathogens that might be the cause of the infection being treated. In the real world, a range of antibiotic regimens have been used to treat patients with CAP. In an international cohort study, more than half of the patients with CAP received β-lactams plus macrolides as an empirical treatment, whereas quinolones and β-lactams alone were the second most likely regimen used (244, 245). A β-lactam alone is less likely to be prescribed for CAP patients. This could be due to expected unfavourable clinical outcomes (244).

The pattern of antibiotic prescribing could be different among regions and countries. In one study, it was found that doctors in Australian hospitals frequently prescribed a β-lactam plus either doxycycline or macrolides for patients who were diagnosed with CAP - as an empirical therapy. A penicillin-based regimen was commonly used (55.8%), and ceftriaxone-based regimens represented 36.8% of cases (210). However, in Europe, doctors more frequently prescribe B-lactam monotherapy than a combination therapy (214).

Antibiotic prescribing practice seems to be influenced by the patient's age. For example, patients aged less than 65 years have been shown to be less likely to receive B-lactam antibiotics and more likely to receive quinolones than older patients (202, 246).

1.6.13. Adherence rate to CAP guidelines' recommendations

The adherence rate to the guidelines for CAP varies greatly from country to country, and even between institutions within the same country. For instance, in one of the largest audit studies in the UK, which included 64 institutions, the overall adherence to the national guideline regarding CAP management was 56% (50% - 70%) (247). On the other hand, in one multi-centre study in Australia that included 26 institutions, the overall adherence to the national guideline regarding CAP was only 20% (220). Although the overall compliance with the national guideline was very low in

Australian hospitals, single institutions could reach very high levels of adherence. For example, in one teaching hospital in Australia, adherence to the CAP guideline was 72.3% while it was as low as 18% in another (220, 248). Compliance with the recommended CAP guideline was seen more in severe cases (220, 247). However, guidelines are less likely to be followed among patients admitted to ICU (249).

Non-concordance to the guideline's recommendations could lead to either under treatment or overtreatment. For instance, in one international study of an elderly population, it was found that around one-third of patients with severe CAP received non-concordant antibiotic regimens that were considered to be under treatment according to the guideline's recommendation. On the other hand, around 60% of patients with moderate CAP received antibiotic treatment that was considered to be overtreatment according to the guidelines (244).

Studies have used different criteria to measure adherence to the recommended guidelines. Several studies have measured adherence to the CAP guideline where the selection of antibacterial agent was based on the severity of CAP (221, 247), while others also considered the route of administration, dose, and presence of penicillin allergy when antibiotics were selected as the additional tools for measuring the rate of adherence (220, 248, 250). Some studies defined adherence to the guideline as any antibacterial regimen that was used according to the guideline regardless of the CAP severity (251, 252). This may explain the unusual variability in the concordance rates observed in the above-mentioned studies.

1.6.14. Barriers towards adhering to the guideline's recommendations

Few studies have assessed the barriers that could hinder the use of the recommended guidelines for the management of CAP. A lack of education and confidence seems to be the main barriers for junior doctors (253). However, the likelihood to council the recommended guideline becomes less as doctors get more experience. Other barriers include the high work load in busy

departments such as ED, and the lack of support from senior doctors. Furthermore, the complexity of CAP guidelines could be one of the reasons for non- adherence (253). Awareness of the presence or change in the recommended guideline could be a major barrier. Almost half of the doctors (48%) in 7 Pittsburgh hospitals, who responded to a survey regarding the barriers towards adhering to the recommended local CAP guideline, were uncertain about the availability of the guideline (254). A lack of familiarity with the guidelines, lack of outcome expectancy, and the presence of other CAP guidelines that conflict with the recommended national CAP guideline were found to be the major barriers to physicians' compliance with the CAP guidelines in a qualitative study (157).

1.6.15. Impact of adherence on clinical outcomes, healthcare costs, and clinical practice

Studies have shown that physicians are more likely to make inaccurate estimation of CAP severity if guidelines are not used, leading to an increase in mortality rates amongst this group of patients (255-258). Several studies have shown that adherence to the recommended guidelines for the management of CAP has clearly improved the process of care and patients' clinical outcomes (257, 259).

A number of studies showed that the survival rate for patients with CAP, who were managed according to the guidelines, was significantly higher than those who were not (169, 258-263). In one large retrospective study (115 institutions) for CAP patients who were not admitted to ICU, the mortality rate decreased significantly from 6.8% to 5.2% when the recommended CAP guideline was used (262). For ICU patients, with an overall mortality rate around 3 times higher than non-ICU patients, compliance with the recommended CAP guideline can markedly reduce the mortality rate from 25% to 11% (264). Arnold *et al.* found that the in-patient and 30-day mortality rate for elderly patients was significantly less when patients with CAP received antibiotic regimens consistent with CAP guidelines' recommendations (8% vs 17%; $p < 0.01$) (244). Concordance to

the guideline significantly increased the survival rate, which could reach 14% higher than those who have not been managed according to the guideline (264).

Adherence to the recommended CAP guidelines has been associated with reduction in hospital LOS among patients with CAP (249, 259, 262, 265, 266). Dambrava *et al.* found that adherence to the national CAP guideline can significantly reduce LOS by two days from 10.4 days to 7.6 days (249) even though LOS for patients with CAP depends on the time needed for the patient to be clinically stable, which is correlated to the severity of the disease (266). The observed reduction in LOS for CAP patients who receive appropriate antibiotic regimens could be attributed to the shorter time needed for patients with CAP to be clinically stable. In their study, Arnold *et al.* showed that the probability for patients with CAP to reach clinical stability within 7 days of admission was significantly higher for patients who received antibiotic regimens consistent with the guideline, which led consequently to a shorter LOS (244). Being recipient of concordant antibiotic regimen for the management of CAP is associated with lower treatment failure. Blasi *et al.* studied the effect of adherence to the national CAP guidelines on the rate of treatment failure; that is, worsening of symptoms or the need to change the antibiotic regimen. The analysis of the outcomes from 2,847 patients showed that adherence to CAP guidelines led to statistically significant reduction in treatment failure (OR 0.74, 95% CI 0.06-0.9) (257). Therefore, overall, it seems that concordance to the recommended guideline can reduce LOS, time to clinical stability, treatment failure, and the rate of hospital admission, which in turn can reduce the healthcare costs of CAP.

Concordance to the guideline can also reduce healthcare costs in several ways. In their analysis of healthcare costs of hospitalisation due to CAP, Menendez *et al.* found that around 70% of the cost of hospitalised patients with CAP were due to the room occupied and LOS (251). In terms of hospital admission, using the recommended scoring tool could help decide if patients need to be hospitalised or not (267). It has been shown that the rate of outpatient treatment for patients with CAP at risk groups I-III increased by 18% when the recommended PSI tool was used (268).

On that ground, it was estimated that more than one billion American dollars would be saved in the US if unnecessary hospital admissions were reduced (269). The estimated cost of treating outpatients with CAP in Australia is $20 million per annum (270). This cost could be doubled if the patients were admitted to hospital unnecessarily, such as in mild cases (271).

Clinical practice has been shown to improve after the implementation of guidelines (259). It was shown that the duration of antibiotic treatment and the time to switch from intravenous antibiotics to oral antibiotics could be reduced by more than two days in severely ill patients with guideline adherence. Alberto *et al.* found that patients who received antibiotic according to the recommended guideline reached clinical stability faster, leading to a rapid switch from intravenous to oral antibiotics. This led to a decrease in the overall duration of antibiotic treatment, which was reduced by more than one day (259).

1.6.16. Initiatives to improve compliance with CAP guidelines' recommendations

Many national and local initiatives have tried to improve the quality of CAP management (248, 250, 272). It has been agreed that there is a positive correlation between adherence to the recommended guideline and reduced LOS and mortality rate. The main effort has been to actively implement the guideline. Studies showed that active implementation of the CAP guideline can significantly increase the rate of adherence. Reported rates of improvement in concordance with the guideline ranged from 6.2% to 28% (250, 257, 272, 273).

It is not uncommon to perform more than one strategy in order to implement CAP guidelines. In one meta-analysis study, it was found that the intervention strategies most often used were educational meetings (63%) and dissemination of written materials (78%) (274). A combination of these two strategies was used in 52% of the studies. Most intervention studies resulted in a modest improvement in the adherence rate to the guideline, except in the case of audit and feedback

strategy, which when used alone resulted in either a lack of or only modest improvement (274). Increasing strategies to be multifaceted for implementing CAP guidelines in an institution has been associated with an increasing utilisation of the recommended guidelines. An American large randomised controlled study showed that the adherence rate in those hospitals, where high intense multifaceted strategies were performed, was significantly higher than those in hospitals where only low or moderate intense strategies were performed (65.6%, 29.3%, and 30.7%, respectively) (275, 276).

Some strategies might be more suited to a particular healthcare setting, such as one-on-one academic detailing which might not be practical in busy areas such as ED, where it could take 12 minutes on average (277). Similarly, ED might not be a good place to conduct one-on-one education due to the small area available. In contrast, group discussion might be more accepted in a busy department (277).Table **1.9** summarises the interventions that have been shown to improve implementation of recommended CAP guidelines:

Table 1.9: Summary of the interventions of recommended CAP guidelines that have been used to improve implementation (274).

Intervention	Intervention methods
Educational	• Dissemination of written materials (e.g. mailing) • Educational meetings (e.g. grand rounds) • Academic detailing (i.e. one-on-one meeting between prescriber and trained medical staff)
Reminders	• Patient chart reminder (i.e. standard treatment in the chart) • Electronic reminder (i.e. appearance of the recommended guideline when ordering) • Pre-printed forms • Undefined reminder (e.g. potters or tag card)
Local opinion leader	
Audit and feedback	• (i.e. feedback of the performance regarding adherence to the guideline throughout period of time)
Multi-participation	• Multidisciplinary team (team from different specialities) • Local consensus process (i.e. including prescribers in the discussion regarding the guideline) • Patient mediated intervention (i.e. third party intervention such as by a pharmacist)
External guiding	• Clinical pathway • Standing order (e.g. preauthorised order set) • Formulary adaption (e.g. limiting antibacterial choices)
Structural	• Computerised system (i.e. decision support) • Organisational (e.g. selected antibiotic stock at the ward)
Other recorded factors	• Quality improvement organisations (i.e. local or external organisations that focus on the improvement of CAP outcome)

Interventions among Australian hospitals

Several efforts and interventions have been made among Australian hospitals to improve the quality of antibiotics use for the management of CAP. One of the Australian programmes for improving the quality of antibiotics use was the Community-Acquired Pneumonia: Towards Improving Outcome Nationally (CAPTION) (250). The programme is aimed at improving the appropriate use of antibiotics in CAP through encouraging physicians to adhere to the national guideline. EDs around Australia (n=26) participated in the programme. The first step of CAPTION was to collect baseline data to measure the rate of adherence to the guideline before any intervention was made. These interventions were mainly educational, which included:

1- One-on-one academic detailing
2- General slide presentation for the feedback of local data on guideline concordance, and an education session about the best practice management of CAP according to the guideline
3- Supply letters to the prescribers
4- Wall posters
5- Tag cards that included PSI variables to be measured

The overall improvement in the adherence to the guideline was moderate, with adherence rates rising from 20% to 30%. However, a limitation of the study was the low number of patients (20 patients in each hospital).

Another intervention was made by one Australian teaching hospital to improve the use of the CAP guideline (248). In this intervention, the guidelines were made easily accessible in the ED and throughout the hospital computer system. Furthermore, physicians were encouraged to calculate and document the PSI on the medical record and to use that to guide patient admission and the use of recommended antibiotics. That study showed that even though it was difficult to apply the PSI in the ED, concordance to the recommended guideline was 20% more when PSI was documented. However, one limitation of the study was the lack of baseline data to measure the effect of the intervention.

The type of intervention could significantly make a difference in the adherence rate. For example, the use of a computer support system could be more effective than academic detailing to implement a guideline. These two strategies were implemented in one Australian hospital in two different periods of time (148). During the first period, one-on-one academic detailing was utilised. In the second period, a computerised system for antibiotic prescribing, where the guideline's recommendations came up on screen at the time of ordering was implemented. The transferable website included tools to calculate the PSI variables in order to guide the admission decision (outpatient vs inpatient), and CURB65 variables in order to decide whether the patient needed ICU

admission or not. The website also included recommendations about appropriate antibiotics, duration, time to switch therapy from IV to oral, and the relevant literature that supported the recommendations. This strategy increased awareness of the guideline and hence adherence. When compared to the academic detailing strategy, the rate of adherence was higher when a computer support system was utilised (68.7% and 89.7%, respectively).

1.6.17. Management of CAP in ED settings

Many guidelines encourage the use of the antibiotics as soon as a diagnosis of pneumonia is confirmed by the chest X-ray (144, 182, 186). Therefore, it is not surprising that antibiotics are more likely to be administrated in the ED before admission to the ward. In one study that was conducted in 1,370 admitted patients with a primary diagnosis of CAP, it was found that nine out of ten patients received their first dose of antibiotics in the ED (278). ED clinicians were likely to prescribe antibiotics to elderly patients more often than to younger patients (278). Furthermore, physicians at the ED were less likely to delay the administration of antibiotics for those patients with high temperature at the time of triage, high respiratory rate, history of cardiopulmonary disease or presence of abnormal chest X-ray. However, confused patients and those present with shortness of breath were less likely to receive antibiotics in the ED (278).

ED would be an optimal place to start for any intervention aiming to enhance adherence to CAP guidelines for several reasons. In a hospital setting, most patients are initially diagnosed with CAP in ED (278). That makes ED the primary source of hospital admission for the vast majority of CAP patients. Furthermore, ED physicians are always encouraged to take timely decision when admitting or sending a patient home in order to avoid a back log of patients in ED and hospital inpatient beds (279). The first dose of antibiotics is more likely to be initiated while the patient is in the ED (278). Furthermore, ED physicians are more likely to overestimate the disease severity of CAP which leads to unnecessary hospitalisation and use of inappropriate antibiotics (275). For all

the above reasons, initiatives to optimise the management of CAP at EDs are likely to improve the appropriateness of CAP management in hospital settings (275).

1.7. Study sites

The Royal Hobart Hospital (RHH) is a principal referral hospital in Tasmania. It has 550 beds serving around 240,000 people in the southern region of Tasmania. It represents a major clinical and research centre in the area, so it works closely with the University of Tasmania (280).

An antimicrobial stewardship programme was officially launched in mid-2009 with the following responsibilities and routine activities (281):

1- Development of antibiotic guidelines.
2- Apply restriction polices for broad spectrum and expensive antibiotics.
3- Perform regular rounds in intensive care and oncology units.
4- Daily rounds to provide feedback on antibiotic prescribing to prescribers.

The North Western Regional Hospital (NWRH), on the other hand, is a 160-bed secondary service hospital that provides services to north western Tasmania and King Island. The distance between the two hospitals is 330 Kilometres. Transfer to other tertiary hospitals might occur for some diseases (280).

1.8. Background and rationale

There have been an increasing number of studies that measure the adherence rates to CAP guidelines' recommendations in hospital settings (257, 282-284). This focus is based on studies that showed a positive impact of adherence to CAP guidelines on clinical outcomes, particularly mortality rates and healthcare costs.

A previous published study showed poor adherence rates to the national CAP guidelines' recommendations for an empirical management of CAP among Australia's

hospitals (220). However, despite the national initiative to increase adherence to the national CAP guidelines, improvement has been limited. A study conducted by Mclntosh et al. in 26 Australian hospitals found that the active implementation of national guidelines for the management of CAP, by means of academic detailing and distribution of educational materials, had only a modest effect on raising the adherence rates to CAP guidelines in ED (30% vs 20%) (250). However, academic detailing was perceived as a time-consuming process, particularly in a busy clinical area such as ED. Since the adherence rate was low even after interventions, addressing factors that hinder the doctors' adherence to CAP guidelines could provide some insights into the most appropriate strategies for actively implementing CAP guidelines. Overall, published studies on the management of CAP either evaluate these factors alone or evaluate the effects of selected interventions without addressing the factors that hinder doctors from adhering to the CAP guidelines.

1.9. Thesis aims and outline

The overall aim of this research project is to develop and evaluate the implementation of the CAP guidelines in an Australian hospital sitting, by tailoring an intervention through addressing potential factors that affect adherence to the same guidelines. The evaluation of the chosen tailored intervention strategies was aimed at measuring the extent to which the intervention would affect adherence rates and consequently clinical outcomes.

Given the nature of studies being examined in this PhD thesis and the plurality of methods used in such studies, each chapter in this thesis will discuss separately the relevant studies' methodology. Each chapter thus represents the results of a particular study that was designed to answer a specific research question(s). Throughout this thesis, the terms adherence and concordance will be used interchangeably to refer to prescribing or receiving medications as recommended by the guidelines.

Chapter 2 (baseline): This chapter will collect and analyse the baseline data retrospectively from both RHH and NWRH in order to measure the adherence rates and characterise antibiotic prescribing for the management of CAP before any intervention.

Chapters 3 and 4 (barriers): In these two chapters, two studies were conducted (quantitative and qualitative) with the main aim of determining the potential barriers and factors that hinder doctors from adhering to the guideline's recommendations towards the empirical management of CAP.

Chapter 5 (enablers): A survey questionnaire was distributed to infectious disease pharmacists in Australian public hospitals. This study was aimed at determining strategies that have been used by institutions and perceived as successful towards improving the empirical antibacterial management of CAP.

Chapter 6 (intervention): The findings from chapters 2, 3, 4 and 5 were utilised to design intervention strategies. In this chapter, we discussed how those findings influence our decision regarding selection of the interventions' component. Furthermore, we discussed the rationales behind the chosen approaches to evaluate the impact of the intervention.

Chapter 7 and 8 (outcomes' evaluation): In these two chapters, we aimed at determining the impact of our intervention strategies on the rates of adherence to CAP guidelines and clinical outcomes (mortality and LOS).

Chapter 9 (outcomes' evaluation): This chapter aimed to show the effect of our intervention on the appropriateness of ceftriaxone prescribing of all indications, including CAP.

1.10. Significance of the research

As a rule, the active implementation of clinical practice guidelines to improve management of CAP is found to be more effective than passive dissemination. However, there are a few published studies that addressed the rationale behind choosing an intervention component. Therefore, to maintain a sustainable effect, a clear understanding of factors and barriers that affect guideline adherence is warranted in order to ensure that clinical prescribing behaviour changes. In this research, we explored these factors in-depth and then designed an intervention component accordingly.

1.11. Limitation of the research

This research only focused on empirical antibiotic management. Therefore, this research project was not designed to evaluate other processes of care indicators such as time to antibiotic and diagnostic measurement.

Chapter 2. Adherence to TG14 recommendations for the empirical management of CAP: baseline study

2.1. Introduction

Two major changes affecting the empirical management of CAP were introduced with the 2010 edition of the Australian Antibiotic Therapeutic Guidelines (TG14) (144). The first related to the recommended severity assessment tool; in the previous CAP guidelines (TG13, 2006), the pneumonia severity index (PSI) was recommended, whereas TG14 advocates the use of the alternative tools, SMART-COP or CORB(144). This change was due to the complexity of the PSI, which requires 20 variables to be considered; in contrast, no more than eight variables are required for use of the SMART-COP and CORB tools.

The second set of changes related to the recommended antibiotic treatment regimens. For instance, roxithromycin was replaced by clarithromycin as a treatment option in TG14. Although there is no specific trial evidence to support this change, the recommendation was based on the consensus opinion of the expert group that roxithromycin is inferior to clarithromycin for the management of lower respiratory tract infections (144). Three IV antibiotics from the penicillin group (benzylpenicillin, amoxycillin and ampicillin) were recommended for moderate CAP in TG13 to cover *S. pneumoniae,* however, this was simplified in TG14, with just IV benzylpenicillin retained. This was on the basis of its narrower spectrum and the reduced potential for associated collateral damage; that is, disturbance of normal bacterial ecology that leads to the development of adverse effects and further increases the emergence of antibiotic-resistant bacteria or (31). TG14 also saw the removal of the previous recommendation to use a combination of antibiotics for the initial management for patients with mild CAP. This change was based on research showing no difference in mortality rate between patients treated with monotherapy and combination therapy (β-lactam/macrolide) (285).

Against the background of these changes to CAP management guidelines, the primary aims of the study were:

- To characterise antibiotic prescribing for patients with CAP at the Royal Hobart Hospital (RHH) and North Regional Hospital (NWRH).
- To assess the concordance between prescribing practice and the TG14 recommendations for the empirical management of CAP.

2.2. Methods

A retrospective study was conducted amongst adult patients (≥ 18 years) admitted to the RHH and NWRH, and diagnosed with pneumonia within 24 hours of admission. A list of patients who were classified as having pneumonia, CAP or lower respiratory tract infection (LRTI) during 1st July 2010 to 31st March 2011 was obtained from the clinical classification and information department of each hospital.

2.2.1. Definition of variables

A patient was considered to have CAP if a diagnosis of pneumonia was made by the physician and documented in the medical notes, or the radiologist or physician referred to the presence of consolidation, infiltration or pneumonia in a chest X-ray report. Empirical antibiotic therapy refers to the first regimen used within 24 hours of admission.

2.2.2. Exclusion criteria

Those excluded from the study were: (i) immunosuppressed patients (on chronic corticosteroids or immunosuppressive agents, chemotherapy within three months before admission, or a history of an immunosuppressive disease, such as HIV); (ii) patients who had been previously admitted to a hospital within 14 days of admission or had been admitted from an aged-care facility (ACF); (iii) patients who did not receive any antibiotic therapy or who had incomplete medical records; and (iv) patients who had a history of cystic fibrosis or bronchiectasis.

2.2.3. Data collection

The criteria for eligibility and guideline adherence were agreed by the research team, and the primary investigator undertook review of medical records to assess eligibility and guideline adherence.

Following exclusions, the medical records of all eligible patients were reviewed to obtain data for clinical characteristics and demographics, enable calculation of Charlson's comorbidity index, the antibiotic regimen used (agents, route of administration, dose and duration), the hospital department where antibiotics were first administered, and any antibiotics documented as being given within the seven days prior to admission. Clinical and diagnostic findings were extracted to calculate SMART-COP and CORB values, and used to stratify cases into mild, moderate and severe groups. Clinical outcome data, such as mortality and LOS, were extracted from the discharge summary. Antibiotics were considered to have been initiated in the ED when the documented time of administration was before the time of transfer to the ward.

2.2.4. Outcome variables

The primary measure was the empirical antibiotic regimen (first regimen administered within 24 hours of admission) for the management of CAP. The antibiotic regimen was considered to be consistent with TG14 recommendations when it was concordant with the following three variables: selection of antibiotic(s), dose, and route of administration, based on the level of CAP severity calculated by the researcher. Furthermore, the administration of a penicillin for a patient with a documented allergy to penicillin was considered to be discordant therapy (Figure 2.1).

The second outcome measure was in-patient mortality rate and LOS. To analyse the LOS, only patients who were discharged to home according to the medical team advice and survived the admission were included for further analysis.

The presence of anyone of the followings:

- Respiratory rate > 30 br/min
- Systolic BP < 90 mm Hg
- O_2 saturation < 92%
- Confusion (acute)
- Arterial or venous pH < 7.35
- PaO_2 < 60 mm Hg
- Multilobar CXR involvement

NO → **Mild CAP**: amoxycillin oral OR doxycycline oral OR clarithromycin oral

Yes ↓

SMART-COP and CORB scores were calculated to assign patients into moderate or severe CAP

CORB		SMART-COP	
Variables	Points	Variables	Points
Confusion	1	Systolic BP < 90 mm Hg	2
O_2 saturation ≤ 90%	1	Multilobar CXR involvement	1
Respiratory rate ≥ 30 br/min	1	Albumin < 35 g/l	1
Blood pressure Systolic BP < 90 mm Hg or Diastolic BP ≤ 60 mm Hg	1	Respiratory rate ≥ 30 br/min	1
		Tachycardia ≥ 125 bpm *	1
		Confusion (acute)	1
		Oxygen low * PaO_2 < 60 mm Hg, or O_2 saturation ≤ 90%, or PaO_2/FiO_2 < 250	2
		PH < 7.35	2

Moderate CAP (SMART-COP score < 5 and CORB score < 2	**Severe CAP** (SMART-COP score ≥ 5 or CORB score ≥ 2)
1- Benzylpenicillin IV PLUS EITHER doxycycline oral OR clarithromycin oral 2- Ceftriaxone IV OR cefotaxime IV PLUS EITHER doxycycline oral OR clarithromycin oral** 2- Moxifloxacin 400 mg oral**	1- Ceftriaxone IV OR benzylpenicillin IV PLUS gentamicin OR cefotaxime IV PLUS (in all cases) azithromycin IV 2- Moxifloxacin IV PLUS azithromycin IV**

Br/min = breaths per minutes, BP = blood pressure, O_2= oxygen, PaO_2 = partial pressure of oxygenation, CXR = chest X-ray, bpm = beats per minutes, FiO_2 = fraction of oxygen in inspired air

Doses: Amoxycillin 1 g; doxycycline 200 mg (mild CAP) and 100 mg (moderate CAP); clarithromycin 250 (mild CAP) and 500 mg (moderate CAP); benzylpenicillin 1.2 g; ceftriaxone 1 g; cefotaxime 1 g; moxifloxacine 400 mg; gentamicin 4 to 6 mg/kg

*For patients ≤ 50 years old the value of tachycardia is ≥ 130; and the oxygenation values are PaO_2 < 70 mm Hg, O_2 saturation ≤ 93 and PaO_2/FiO_2 < 333

** Only recommended in case as an alternative regimen for patients with penicillin allergy

Figure 2.1: Stratifying patients into different management groups based on severity as per TG14 (144).

2.3. Results

2.3.1. Patients' characteristics

A total of 276 patients from RHH and 68 patients from NWRH were assessed for eligibility. Of these, 83 patients from RHH and 15 patients from NWRH were excluded. Reasons for exclusion are summarised in Table 2.1.

Table 2.1: Reasons for exclusions from the study.

Exclusion criteria	Number of patients	
	RHH (n=83)	**NWRH (n=15)**
Hospital admission in the previous 14 days	21	5
Immunosuppressed patients	38	7
Admitted from ACF	22	1
No antibiotic prescribed	2	2

Table 2.2 summarises the demographics, documentation of penicillin allergy and CAP severity assessment tool used, CAP severity classes and clinical outcomes for the eligible patients.

With regard to the severity assessment tools, all CORB variables were recorded for all study patients; however, the laboratory and radiological tests required to use SMART-COP, were not always undertaken, in these cases the missing variables were considered as zero points.

Table 2.2: Patients' demographics, characteristics and clinical outcomes.

	RHH	NWRH
Number of patients	193	53
Gender (male)	105 (54.4)	30 (56.6)
age	71 (18 – 96)	70 (20 – 95)
Charlson's comorbidity index score [a]	5 (0 – 13)	4 (0 – 8)
Change in chest X-ray as defined by the radiology report	117 (60.6)	27 (50.9)
Mild CAP	64 (33.2)	31 (58.5)
Moderate CAP	82 (42.5)	9 (17)
Severe CAP	47 (24.4)	13 (24.3)
CORB = 0 point	73 (37.8)	28 (52.8)
CORB = 1 point	82 (42.5)	12 (22.6)
CORB ≥ 2 points	38 (19.7)	13 (24.5)
Prior antibiotic/s within 7 days of admission	43 (22.3)	8 (15.1)
Documented penicillin allergy	30 (15.5)	8 (15.1)
Admission via ED	191 (99)	52 (98.1)
LOS in days		
Overall	4 (1 – 36)	5 (1 – 25)
Mild CAP [a]	3 (1 – 30)	4 (1 – 25)
Moderate CAP	4 (1 – 26)	6 (2 – 9)
Severe CAP	5 (1 – 36)	5 (1 – 15)
In-hospital mortality rate		
Overall	19 (9.8)	1 (1.8)
Mild CAP	-	-
Moderate CAP	5 (6.1)	-
Severe CAP	14 (29.8)	1 (7.7)

2.3.2. Documentation of severity score utilisation

The use of any severity assessment tool was documented in only 9.4% of cases at RHH and in no cases at NWRH (Table 2.3). At the RHH, CURB65 and PSI were the tools most commonly documented (3.7% and 4.9%, respectively); use of either TG14 recommended tool (SMART-COP or CORB) was less than 1%.

Table 2.3: Documented utilised severity tools in RHH and NWRH.

Documented severity assessment tool	RHH N (%)	NWRH N (%)
CURB65	9 (3.7)	-
PSI	12 (4.9)	-
SMARTCOP	2 (0.8)	-

2.3.3. Empirical antibiotic prescribing

Three major classes of antibiotics were frequently utilised to treat patients with CAP: beta-lactams, macrolides and the tetracycline, doxycycline (Table 2.4). Overall, penicillin-based therapy was most commonly utilised at the RHH (52.9 %). In contrast, patients at the NWRH most commonly received ceftriaxone-based therapy (64.2%). Of the macrolides, roxithromycin and azithromycin were the most commonly used at both study sites.

Table 2.4: Frequencies of prescribed antibiotics at the RHH and NWRH for the empirical management of CAP.

Antibiotics			RHH N (%*)	NWRH N (%*)
Beta-lactams				
Ceftriaxone - based therapy	Ceftriaxone		71 (36.8)	34 (64.2)
Penicillin - based therapy	Benzylpenicillin		53 (27.5)	3 (5.7)
	Amoxycillin	Oral	16 (8.3)	-
		IV	33 (17.1)	5 (9.4)
Other beta - lactam based therapy	Cefazolin		3 (1.6)	-
	Cephalexin		1 (0.5)	-
	Flucloxacillin		2 (1)	1 (1.9)
	Amoxycillin + Clavulanate		5 (2.6)	2 (3.8)
	Ticarcillin + Clavulanate		1 (0.5)	2 (3.8)
	Piperacillin + Tazobactam		-	1 (1.9)
Tetracycline	Doxycycline		55 (28.5)	8 (15.1)
Macrolides	Roxithromycin		43 (22.3)	14 (26.4)
	Clarithromycin		4 (2.1)	-
	Azithromycin		35 (18.1)	12 (22.6)
Fluoroquinolones	Moxifloxacin		5 (2.6)	2 (3.8)
	Ciprofloxacin		-	2 (3.8)
Aminoglycosides	Gentamicin		4 (2.1)	2 (3.8)

* As some patients received more than one antibiotic; the percentages do not add up to 100%

A wide variety of different antibiotic regimens were used for empiric treatment of patients with CAP, 29 at RHH and 19 at NWRH. Figure 2.2 shows the most commonly prescribed regimens at the two study sites. As can be seen, the combination of benzylpenicillin and doxycycline was the most commonly prescribed regimen for patients with CAP at the RHH (16.6%), while it was rarely prescribed at the NWRH (1.2%). Ceftriaxone monotherapy was the most commonly prescribed regimen at the NWRH (20.8%).

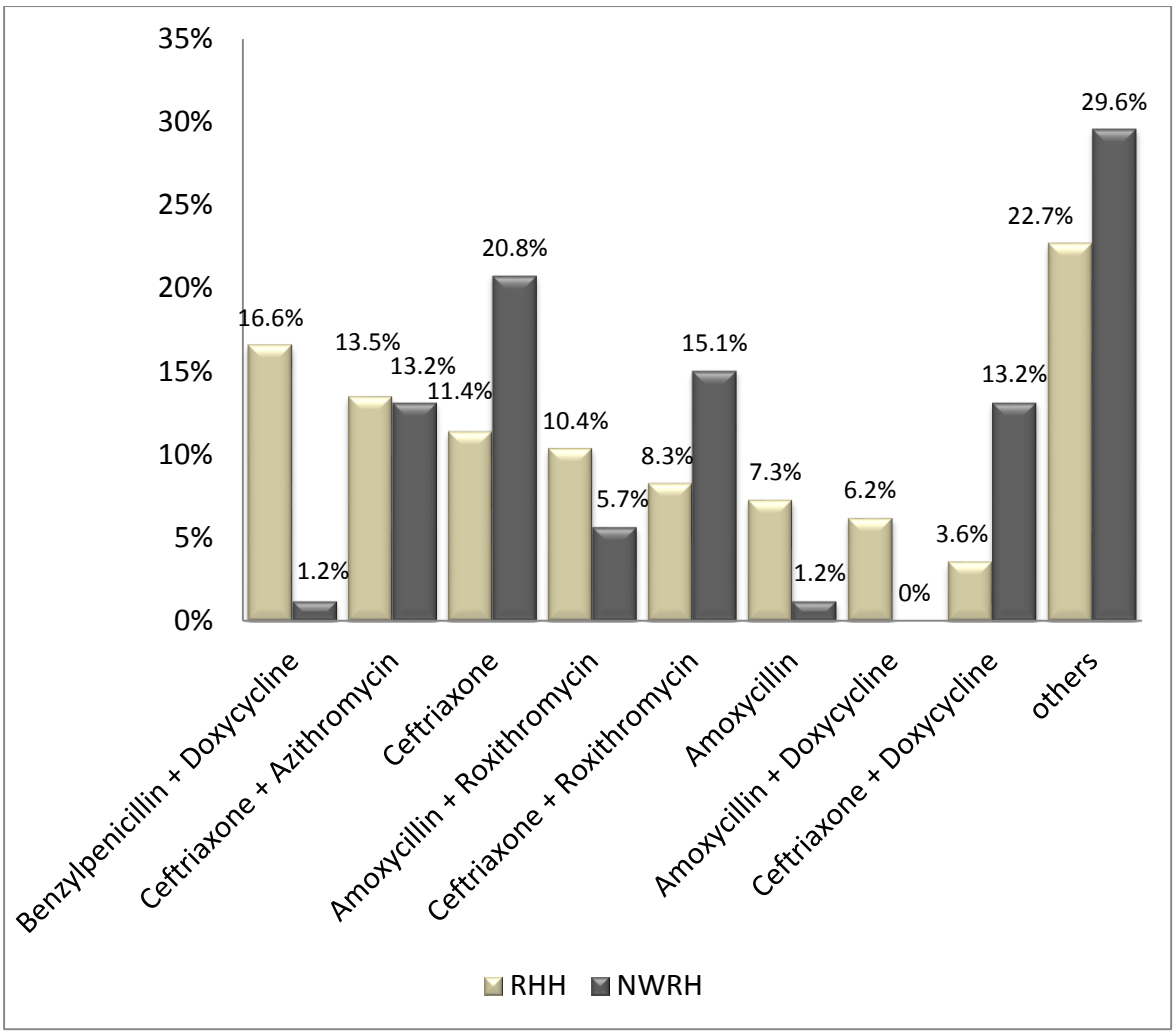


Figure 2.2: Prescribed regimens for empiric management of CAP at RHH and NWRH

When stratifying patients into severity groups, the combination of benzylpenicillin and doxycycline was frequently prescribed to patients with non-severe CAP at the RHH (19.2%) and a combination of ceftriaxone and azithromycin was the most frequently prescribed regimen for patients with severe CAP (57.4%). In NWRH, ceftriaxone regimens were often prescribed, mostly as a mono-therapy for patients with non-severe CAP (20%) and as mono-therapy or in combination with doxycycline for patients with severe CAP (23.8% and 23.8% respectively).

While there was no significance deference in ceftriaxone prescribing amongst severe cases between the two hospitals, the overall prescription rate of ceftriaxone was almost twice as high at NWRH compared to the RHH($p < 0.001$).

Within study sites, ceftriaxone-based therapy was more likely to be prescribed for those patients with severe CAP at the RHH (57.4%; $p < 0.05$). However, the use of ceftriaxone at NWRH did not appear to be significantly affected by severity of CAP, with rates in severe and non-severe CAP of 69.2% and 62.5%, respectively (Table 2.5).

Table 2.5: Ceftriaxone-based therapy prescribing pattern by severity.

ceftriaxone-based therapy by severity	**RHH N (%)**	**NWRH N (%)**
Overall [a]	71/193 (36.8)	34/53 (64.2)
Severe CAP	27/47 (57.4)	9/13 (69.2)
Non – severe CAP [a]	44/146 (30.1)	25/40 (62.5)

[a] P value < 0.05

2.3.4. Concordance with TG14 guidelines

The overall rates of concordance with TG14 for the management of CAP were 16.1% and 7.5% for RHH and NWRH, respectively. At the RHH when patients were stratified by severity, the concordance to the guideline was found to be 3.1%, 20.7% and 25.4% for patients with mild, moderate and severe CAP, respectively ($p < 0.01$). At the NWRH, only 4 patients received a concordant regimen Figure 2.3).

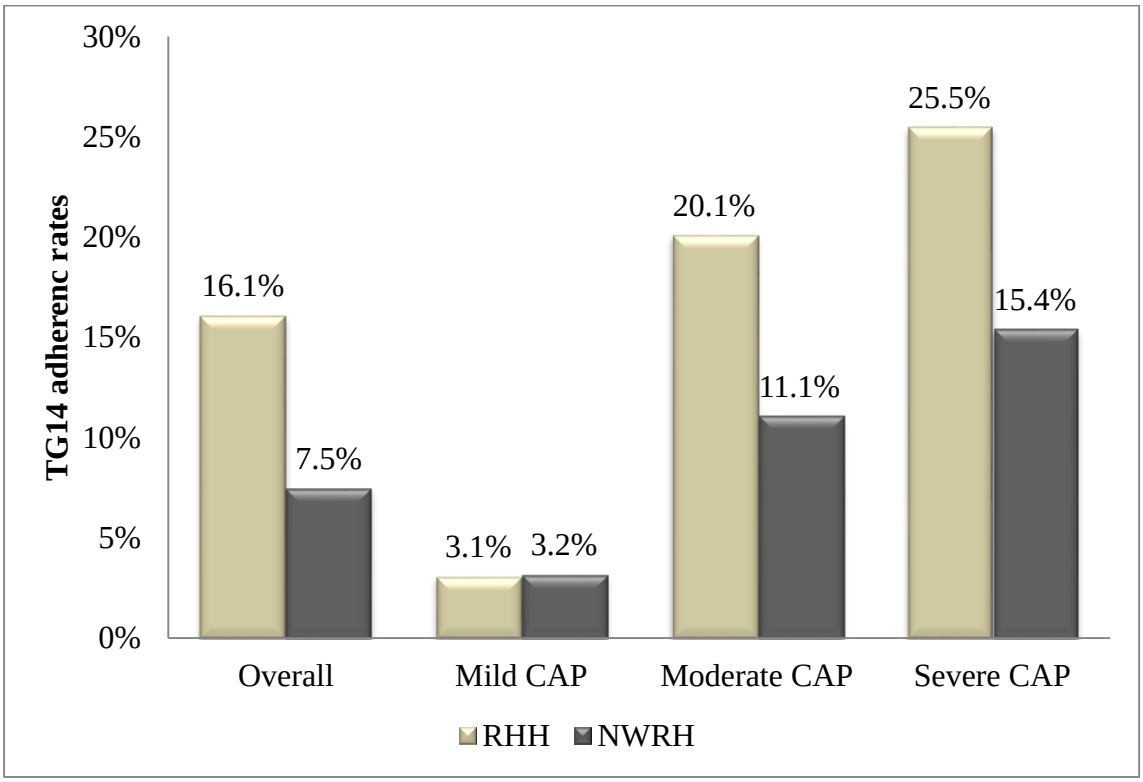


Figure 2.3: Adherence to TG14 recommendations for the empirical management of CAP in RHH and NWRH collectively and by severity.

2.3.5. Alteration of antibiotic regimen within the first 24 hours of the initial administrated regimen

Around half of all patients in both hospitals (56.5% at the RHH and 49.1% at the NWRH) had changes made to their antibiotic regimen within 24 hours of the first dose. (Table 2.6).

Table 2.6: Change of antibiotic regimen within 24 hours of the first administrated regimen.

	RHH	**NWRH**
	N (%)	**N (%)**
Overall	109/193 (56.5)	26/53 (49.1)
Mild CAP	30/64 (46.9)	15/31 (48.4)
Moderate CAP	48/82 (58.5)	4/9 (44.4)
Severe CAP	31/47 (66)	7/13 (53.8)

2.4. Discussion

The most notable finding was the low level of concordance with the CAP management recommendations in TG14. Poor adherence to national guidelines for CAP is not new in Australia and persists despite efforts to address this. A previous study conducted in 37 Australian hospitals, including the two sites in this study, found that overall concordance with national CAP guidelines was only 18% (220). However, despite follow-up efforts to improve adherence to CAP national guidelines, only 10% rise in the adherence rate was seen from 20% to 30% (250).

Adherence to CAP guideline recommendations varies from country to country and between institutions within the same country. For instance, a large UK study found concordance rates across 64 institutions ranged from 50% to 70% (247), which is higher than that seen in our study. Furthermore, while our study shows poor concordance with the national guidelines in both study sites, another Australian study that was conducted in a single tertiary hospital reported a relatively high concordance rate of 72.3% (248). This higher concordance could have been due to the efforts made by the hospital to improve the documentation of the severity tools and stratify patients into severity classes. As can be seen from our study, the adherence to the guidelines varied greatly between two sites within the same state. Whilst the RHH has had an established AMS program since 2009 and no such program existed at the NWRH at the time of the study, this may not provide an explanation for this variation. The reason for this is that the RHH AMS program has been focused on inpatients and consequently ED medical staff may have missed out on the opportunities to improve prescribing inherent in exposure to AMS initiatives. This may be particularly significant in terms of CAP management as the vast majority of patients with this condition received their first dose of antibiotics while in ED. This may result his might explain why adherence to the TG14 recommendations for CAP management, remained poor at the RHH despite the presence of an

AMS program at that site. Nonetheless, as a central aim of AMS programs is to reduce inappropriate use of broad-spectrum antibiotics, such as ceftriaxone, the absence of any such program at the NWRH may explain why ceftriaxone prescribing at the NWRH was significantly higher than at the RHH. However, it is important to bear in mind that limiting the use of ceftriaxone does not ensure adherence to the recommended guidelines.

Published studies have used different criteria to measure the adherence to the recommended guidelines. Several studies measured the adherence to CAP guidelines solely in terms of the selection of antibacterial agent based on the severity of CAP (221, 247); while others, including our study, also considered the route of administration and presence of penicillin allergy when assessing the rate of adherence (220, 248, 250). For example, some studies defined adherence to the guideline without consideration of CAP severity (251, 252). This may explain why the adherence to guideline recommendations varied significantly between previous studies.

Guidelines have been developed in an attempt to optimise CAP management and, when adhered to, these have been shown to be associated with better clinical outcomes (286). Key aspects of the guidelines include assessment of CAP severity and the rational use of antimicrobials (144, 182, 186). It has been found that if guidelines are not used, physicians are more likely to inaccurately estimate the severity of CAP, which is associated with an increased risk of mortality amongst those patients (287, 288). Physicians who do not adhere to guidelines may in some cases select an unnecessarily broad spectrum antimicrobial regimen or in other cases a regimen insufficient to treat the most likely CAP pathogens (244). It has been reported that *S. pneumoniae* is the main bacterial pathogen causing CAP in Australia. Furthermore, Charles *et al.* found that *S. pneumoniae* resistance to penicillin was infrequent in the study samples (210). These findings suggest that the vast majority of CAP patients in Australia could be treated successfully with penicillin-based therapy and this is reflected in the

TG14 recommendations for mild to moderate cases of CAP. This conflicts with current clinical practice where ceftriaxone-based therapy appears to be commonly prescribed as empirical therapy for CAP patients, irrespective of severity. TG14 recommendations are that broader spectrum antibiotic therapy should be used as the severity of CAP increases (144), nonetheless cover should be provided against *S. pneumoniae* in all severity groups. Coverage of atypical pathogens is optional in mild cases, but mandatory in moderate to severe cases. For patients with severe CAP, coverage should also be extended to include gram-negative bacilli. However, it was not uncommon that patients with severe CAP received ceftriaxone mono-therapy, which does not provide coverage toward atypical pathogens. Our study also found that around four out of ten patients with severe CAP at the RHH received penicillin-based therapy, which does not provide coverage against gram-negative bacilli. On the other hand, ceftriaxone based-therapy was frequently utilised for patients with non-severe CAP, where narrower spectrum antibiotics, such as penicillin-based therapy, could provide the necessary coverage for the most likely bacterial pathogens in this group of patients (210). In short, our study found that non-adherence to CAP guideline recommendations included over treatment in some cases and under treatment in others.

This study found the use of a severity scoring tool was rarely recorded in medical notes. A closer look at the data indicates that even when a severity score was documented, the TG14 recommended tools (SMART-COP/CORB) were those least often utilised, whereas other severity tools such as CURB65 and PSI were used more frequently. A recent Australian study showed even poorer documentation of severity tools, where only one out of 69 patients had a severity score documented (289). Several scoring systems have been developed in order to stratify patients according to severity of CAP (234, 235). In one Australian study, it was shown that patients who had a severity score documented in their files were more likely to receive concordant antibiotic regimens compared to those who did not (248). Furthermore,

documentation of severity tool use may help inform other team care members of the rationale for treatment decisions. In our study, a wide variety of antibiotic regimens were utilised and these were often outside TG14 recommendation, irrespective of any consideration of severity level. Therefore adhering to guideline recommendations would limit the wide variety of prescribed antibiotic regimens.

A variety of barriers may hinder clinicians from adhering to the clinical practice guidelines(151). One of the main barriers relates to knowledge, which may include a lack of awareness or lack of familiarity with the guidelines, including changes introduced in the most recent edition of guidelines, in this case specifically TG14. For example, nearly half of the doctors (48%) who responded to a US survey regarding the barriers to adherence with CAP guidelines, were uncertain about the availability of the guideline (254). This may also be true in our study since almost a quarter of the patients received roxithromycin as part of their treatment regimen despite removal of this macrolide from the TG14 recommendations for CAP management.

Changing established prescribing practice is recognised as a significant challenge, and it could be argued that as our baseline study took place soon after the introduction of TG14, clinicians may not have had an opportunity to embrace the new guidelines. However, the TG14 recommendations regarding ceftriaxone use in CAP were unchanged from TG13, with this drug only recommend as a first-line therapy in severe CAP in both editions of the guidelines. In our study 30.3% and 62.5% of cases of non-severe CAP in RHH and NWRH were treated with a regimen that included ceftriaxone. These findings suggested that even if the doctors were not aware of the new guidelines, there may also have been poor adherence to recommendations in the previous guidelines.

Lack of awareness and familiarity with the updated guidelines may have been another barrier. In a qualitative study, it has been found the junior doctors were less familiar with

guideline recommendations compared to senior doctors (165). This barrier to adherence might simply reflect the fact that familiarity with guidelines is acquired with accumulated experience or be due to junior staff having difficulty in accessing guidelines whilst working in busy hospital environments. This latter explanation is however unlikely to apply at either of our study sites where TG14 recommendations are readily available to staff via the hospital intranet. However, it is possible that despite the good availability of guidelines, doctors, especially juniors, may not have been aware of how to find them in their work place.

Our study also indicated that almost half of the antibiotic regimens were altered within 24 hours of the initial dose. These findings appear consistent with other Australian research which found that in most cases, only a single dose of a ceftriaxone-based regimen was given in the ED and this was not continued after the admission (168). Several reasons might lead to this change. Firstly, doctors subsequently involved in the patient's care might differ in their assessment of CAP severity as discussed above. Since the severity assessment criteria were rarely documented, medical staff reviewing the patient after initial assessment might change the antibiotic regimen based on his or her clinical judgment since the rationale behind using an antibiotic regimen is not documented. In our study, we assessed the severity of CAP using the TG14 recommendation severity assessment criteria. However, doctors might use other ways to assess the severity. For example, a patient who is allocated into the severe CAP category based on the TG14 criteria might be stratified into another severity group when another method to assess the severity is used. Secondly, antibiotic prescribing could be initiated by junior doctors, who are most likely to be the first doctor to assess the patient in the ED. It has been found that junior doctors feel less confident when prescribing antibiotics and hence required higher levels of assistance in choosing an appropriate antibiotic regimen (165). Given the short time frame for junior doctors to make decisions in the ED, they might not have time

to consult with seniors regarding the antibiotic choices and this may lead to a change in the initial regimen when the patient is subsequently reviewed by more senior staff.

Furthermore, almost half of the patients were diagnosed as having pneumonia with no supporting evidence from a chest X-ray. Published studies found that ED physicians are more likely to diagnose and treat patients with pneumonia even when the radiologist report indicates normal chest X-ray (290, 291). However, although this may be considered inconsistent with best practice according to published guidelines (144), it should be acknowledged that a chest X-ray may fail to identify changes in almost 30% of patients with clinical presentation of pneumonia (292). On that basis, and given that the main purpose of this study was to evaluate prescribing practice, we included those patients with a documented diagnosis of pneumonia even if this was not supported by radiological evidence.

2.5. Limitations

There are several potential limitations applicable to our study. Firstly, this study collected data commencing just one month after TG14 was released; therefore, prescribers may not have been aware of the changes made regarding CAP management recommendations. However, the total duration of the study was 9 months and there was no evidence of a significant change in guideline concordance over that timeframe. Furthermore, the study was done to collect the baseline data for a longitudinal project aiming to improve the management of CAP and therefore, it was important to identify concordance with the most up to date guidelines to inform future interventions. In our study, patients who were admitted from an ACF were excluded. This is based on the literature which suggests the most common CAP pathogen amongst ACF residents is *Methicillin Resistant Staphylococcus aureus,* in contrast to *S. pneumoniae* for those who are community dwelling (293, 294). Furthermore, this study relied solely on a scoring system to identify patients with severe CAP and TG14 recommends the use of clinical judgment to supplement the use of severity tools. Therefore, patients with non-severe CAP based on use of SMART-COP/CORB severity tools might have been considered candidates for broader-spectrum therapy based on the clinicians' judgment. Additionally, the absence of data required to calculate severity using SMART-COP was interpreted as indicating that parameter was normal. Although we acknowledge this approach might reduce the sensitivity of any scoring system, this approach is consistent with that used in the original study where the SMART-COP tool was developed (234). This approach was also used by Fine *et al.* who developed the alternative PSI severity tool (223). Furthermore, the use of severity tool was very limited in this study and any relative underestimation of severity had minimum effect on overall results.

2.6. Conclusion

Our baseline data showed that concordance with national CAP guidelines (TG14) was poor in both study sites and that ceftriaxone is over-used in non-severe CAP. Based on these findings an investigation into the barriers to guideline adherence is warranted. Such an investigation would provide much needed insight into possible strategies to improve adherence to CAP management guidelines.

Chapter 3. Perceived barriers to Antibiotic therapeutic guidelines (TG14) for the empirical management of CAP

3.1. Introduction

Previous studies showed that adherence to CAP guidelines was historically very low in Australian hospitals (168, 220). However, even after national initiatives to enhance the management of CAP, the improvement in the adherence rate was only modest (250). Consistent with this, the data we have reported in Chapter 2 provides strong evidence that adherence to national guidelines (TG14) for the empirical management of CAP in two Tasmanian hospitals remains sub-optimal. In particular, ceftriaxone prescribing was frequently inconsistent with the guideline recommendations.

A number of barriers have been reported to influence clinicians' concordance with practice guidelines (151, 163, 295, 296). Barriers to guideline adherence differ from one institution to another (166). Therefore, it is important to assess and identify the specific barriers to adherence in any given hospital before designing an intervention to improve antibiotic prescribing in that institution (297). It has been shown that developing intervention strategies that are based on the identified barriers are more likely to improve adherence to guidelines (153).

The purpose of this study was to collect information about barriers related to clinicians' adherence to CAP guidelines at the Royal Hobart Hospital (RHH) in order to inform the development of specific interventions to improve CAP management at that site.

The specific aims of this study were:

- To identify and quantify potential barriers that may hinder doctors' use of TG14 for CAP management at the Royal Hobart Hospital (RHH)
- To ascertain RHH doctors' perceptions regarding the reasons why ceftriaxone is not recommended routinely for CAP management.

3.2. Methods

3.2.1. Study population

Doctors within the general medical teams and ED at the RHH were surveyed for this study. This group of doctors was chosen because of their involvement in the management of patients admitted with CAP. Paper surveys were distributed to a total of 130 doctors via each staff member's hospital internal mail system. A reminder note and additional copy of the survey were sent to all the doctors one month after the initial distribution.

3.2.2. Survey questionnaire

A pool of 20 questions was initially constructed based on the framework of Cabana *et al.*, which classified the barriers to guideline adherence into three groups: knowledge, attitude, and external barriers (151). These were then reviewed by the RHH Antimicrobial Stewardship Team (Infectious disease physician, clinical microbiologist, and specialist clinical pharmacist), who made recommendations to modify and refine the question pool for local application.

The final survey consisted of two main sections to identify potential barriers: the first consisted of three statements to assess doctors' familiarity, agreement with, and access to TG14 (Appendix B). The second section consisted of ten statements to ascertain doctors' views regarding factors that hinder their peers from adhering to TG14 when managing CAP. A 5-point Likert-type scale was used for the 13 statements. Additionally, doctors were asked a number of specific questions regarding , their understanding of why ceftriaxone is not recommended for the majority of CAP cases based on six pre-defined statements; and the tool(s) that they routinely use to assess the severity of CAP in individual patients; . Respondents were also asked to provide details of their seniority (intern, resident, registrar or consultant) and their work location (emergency department or general medicine).

3.2.3. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows software (version 19.0. Armonk, NY: IBM Corb19). Chi-square and Fisher's exact tests were used to assess the significance between categorical data. Fisher's exact test was used if one of the expected values had less than five participants. The responses regarding knowledge, attitude and external barriers toward TG14 were grouped into three classes: strongly agree/agree responses were combined to indicate agreement with the statement, neutral, and strongly disagree/disagree responses were combined to indicate disagreement with the statement. A P-value < 0.05 was considered statistically significant.

3.3. Results

3.3.1. Demographic profile

Of the 130 emergency department and medical team prescribers who were sent the survey, 56 responded (rate of 43.1%). Of these, 21 responses were from the emergency department (6 juniors and 15 seniors) and 35 responses from medical teams (15 juniors and 20 seniors). The term junior was used to refer to interns and residents, while the term senior refers to registrars and consultants.

3.3.2. Barriers to adherence to CAP guidelines

Table **3.1**summarises the level of agreement with statements regarding potential barriers that hinder medical staff from adhering to TG14 with regard to CAP management.

Table 3.1: Percentage of agreement with the statements regarding the barriers that could hinder adherence to TG14.

	Total	Hospital department [a]		Medical staff seniority	
	N = 56	ED	MT	Junior	Senior
		N = 21	N = 35	N = 21	N = 35
Thoughts regarding the possible barriers that hinder other doctors from adhering to the TG14 CAP guidelines					
• **Influence of senior doctors**	26 (46.4)	12 (57.1)	14 (40)	16 (76.2) [b]	10 (28.6) [b]
• **Lack of awareness**	22 (39.3)	9 (42.9)	13 (37.1)	3 (14.3) [b]	19 (72.2) [b]
• **Calculation requirement to assess the severity**	20 (35.7)	9 (42.9)	11 (31.4)	4 (19) [b]	19 (54.3) [b]
• **Existence of other guidelines that conflict with TG14**	16 (28.6)	9 (42.9)	7 (20)	5 (23.8)	11 (31.4)
• **Not expected to follow the guidelines**	13 (23.2)	5 (23.8)	8 (22.9)	4 (19)	9 (25.7)
• **Lack of time**	12 (21.4)	4 (19)	8 (22.9)	9 (42.9)	3 (8.6)
• **Interference with doctors' autonomy**	6 (10.7)	3 (14.3)	3 (8.6)	2 (9.5)	4 (11.4)
• **Impractical to implement**	3 (5.4)	-	3 (8.6)	2 (9.5)	1 (2.9)
• **Not sufficiently evidence-based**	2 (3.6)	1 (4.8)	1 (2.9)	1 (4.8)	1 (2.9)
• **Not clear**	2 (3.6)	1 (4.8)	1 (2.9)	1 (4.8)	1 (2.9)

Data are presented as number (%).
[a] ED : emergency department; MT: medical teams
[b] *P* value < 0.05

When the participants were asked about their familiarity, agreement and access to TG14 in terms of CAP management, the majority reported self-familiarity and agreement with the guideline' recommendations with no problems regarding accessibility to TG14 at workplace (Figure **3.1**).

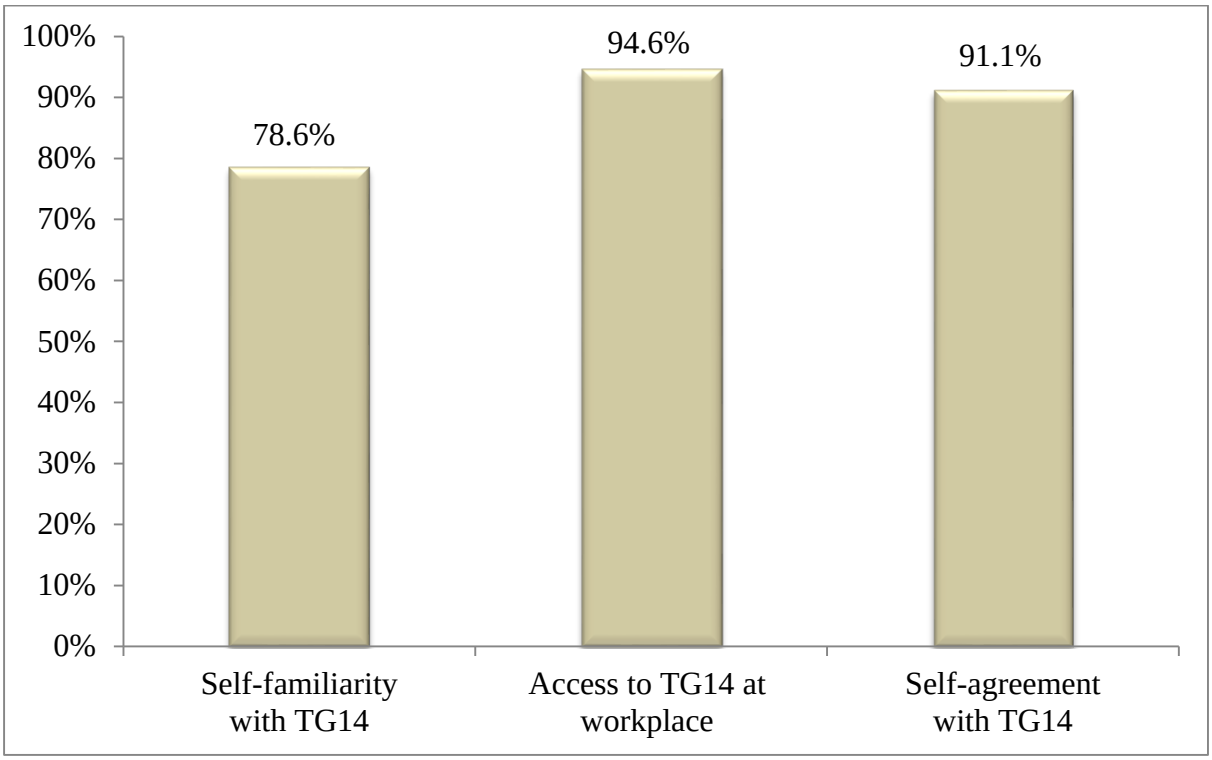


Figure 3.1: Summary of responses regarding familiarity, agreement with, and access to TG14.

The majority of participants reported that they were familiar with the TG14 (78.6%) and there were no differences observed in terms of seniority or the area of practice (Figure **3.1**). Interestingly, nearly half of the respondents (39.3%) thought that the lack of awareness of the guidelines could be a reason for their fellow doctors' non-adherence.

While there was a high rate of self-reported agreement with the TG14 recommendations (91.1%), the main barriers relating to attitude were the view that the hospital did not expect its staff to use the guidelines (23.2% agreement).

In the case of external barriers, the vast majority of the respondents (94.6%) reported that they had access to TG14 in their workplace. The major reason cited for hindering adherence to the guidelines was the influence of senior physicians. Almost half of the respondents (46.4%) thought that prescribing was largely under the direction of senior doctors. The requirement to calculate CAP severity was acknowledged as a barrier by 35.7% of the respondents. Just over quarter of the respondents (28.6%) reported that the presence of other CAP guidelines that conflict with TG14 as a potential barrier.

Responses to these questions varied according to the level of medical staff seniority. For example, senior doctors were more likely than their junior colleagues to think that the lack of awareness of TG14 (72.2% vs14.3%; $p < 0.05$) and the need to calculate severity (54.3% vs19%; $p < 0.05$) were the main reasons for the non-adherence. On the other hand, junior doctors thought that the influence of the senior doctors was the main reason for non-adherence to the guidelines (76.2% vs28.6%; $p < 0.05$).

3.3.3. Perception about why ceftriaxone is not recommended for most patients with CAP

Figure **3.2** shows that three reasons were commonly identified as why ceftriaxone is not a good choice for the majority of CAP cases: penicillins give the same results in most cases (86.4%), many cases are not severe (79.5%), and the risk of multi-drug resistance (77.3%).

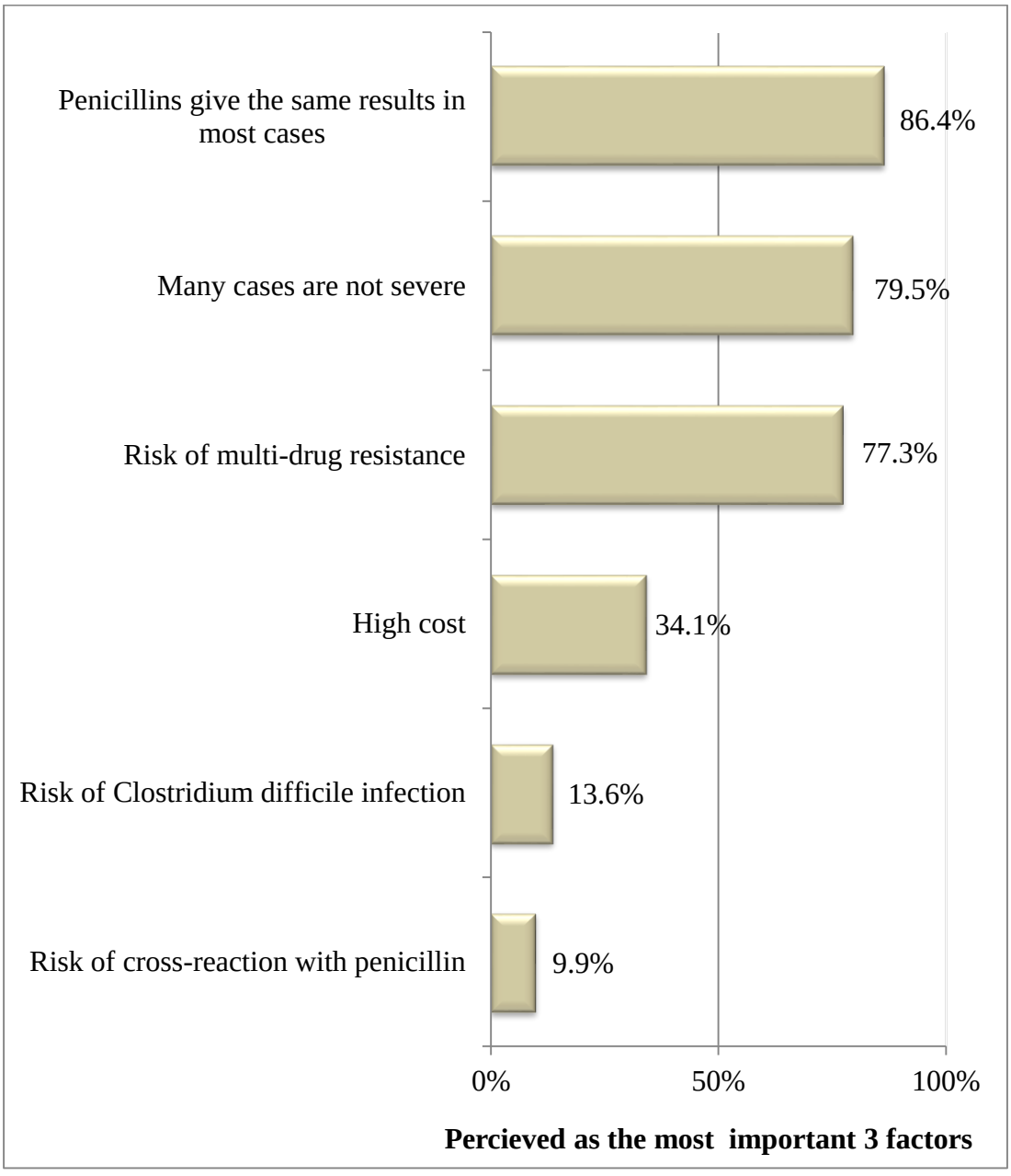


Figure 3.2: Respondents perceptions of why ceftriaxone is not recommended for the majority of CAP cases.

3.3.4. Self-reported use of CAP severity assessment tool(s)

In response to the question 'Which tool(s) do you use to assess the severity of CAP?', different severity tools were utilised with only five participants reported non-use of any tool as shown in Table 3.2.

Table 3.2: Self-reported tool(s) use to assess the severity of CAP.

Self-reported severity tool use	N (%)
CURB65	31 (55.4)
PSI	20 (35.7)
SMART-COP	20 (35.7)
CORB	6 (10.7)
No tool used	5 (8.9)

Table does not add up to 100% because some respondents reported the use of more than one tool.

3.4. Discussion

This study Identified that a number of barriers affect doctor's adherence to the recommendations in TG14 for management of CAP at the RHH. The influence of senior doctors, lack of awareness, the requirement to undertake a calculation to assess the severity of CAP, existence of other guidelines that conflict with TG14, and not being expected to follow the guidelines were the most commonly cited barriers.

In general, the survey showed that doctors had a positive attitude toward the recommendations in the CAP guidelines, which is consistent with other studies (298). However, despite this, practice reflected poor adherence to the guidelines as shown in the baseline study. Moreover, despite most doctors reporting familiarity with, and ease of access to, the guidelines in practice; few doctors reported the use of the recommended severity assessment tools. This was also consistent with our baseline data, where the use of these tools was rarely documented in the medical notes, and where tools were used; they were often not the ones recommended in TG14 (section 0). Linder *et al.* found that doctors who reported being more familiar with the guidelines for the management of acute respiratory infections were more likely to prescribe discordant antibiotics (299). These findings, together with our study, suggest that the reported familiarity does not always translate into adoption of recommendations in clinical practice The most notable barriers found by our present study were the influence of senior doctors and a lack of awareness of a new version of the guidelines. However, according to our data, the perception of these two barriers was noticeably different between senior and junior staff. While the influence of senior doctors was the most frequently reported by junior physicians, senior physicians thought that the lack of awareness was the main explanation of poor adherence to the CAP guidelines. These two barriers have been the principal findings in quantitative and qualitative studies that looked at barriers to adherence with clinical guidelines (161, 163, 295, 296). As our study was

conducted in a teaching hospital, it is highly likely that the first doctor to see a patient will be a junior. Junior doctors are more likely to be influenced by the prescribing habits of their seniors and supervisors (161, 163, 295, 296). Pieter-Jan *et al.* confirmed this finding in their qualitative study where junior doctors considered their supervisors as a role model with regard to antibiotic prescribing, which as a consequence determined their prescribing behaviour (161). Senior doctors, on the other hand, are more likely to rely on their clinical judgment to assess the individual case and guide the choice of antibiotics (163). In a qualitative study looking at factors influencing antibiotic prescribing in a 500-bed teaching hospital, it was found that personal experience become the major influence in antibiotic prescribing with career progress (295). Our data suggest that junior doctors strongly believe that the influence of senior doctors might be the major determinant of their antibiotic prescribing habits, unlike senior doctors who thought the lack of awareness of the guidelines might be the main reason behind prescribing discordant regimens.

Despite the high level of self-reported familiarity with the new version of the guidelines, lack of awareness was the most commonly stated barrier that might contribute to low adherence with CAP guidelines according to the responding senior doctors. This is consistent with a recent Australian study that found a lack of knowledge and awareness of recommendations to be the major barriers to clinicians' concordance with guidelines (300). Influence of the national guidelines for the management of CAP was low according to the study by Switzer *et al.*. (254). In their study, they found that more than half of the surveyed doctors reported that they had not seen the guidelines. Prescribing guidelines, including those for antibiotics, are revised regularly based on the latest evidence-based literature. However, the revised version may not always reach the clinicians who are meant to use them, due to ineffective methods of distributing guidelines. Van Kasteren *et al.* found that the main reason for non-adherence to local antibiotic guidelines for surgical prophylaxis was a lack of

awareness regarding the revised versions (301). This might be more problematic with hospitals that have no local guidelines and rely solely on national guidelines. At the time of the survey, there were no local CAP guidelines at the study site, and the physicians were expected to follow the Australian national Therapeutic Guidelines. Nevertheless, lack of awareness might be one of the main reasons for non-adherence to the TG14 at the beginning. This was clear in our baseline study since the macrolide antibiotic, roxithromycin, was frequently prescribed for CAP management despite being absent from guideline recommendations.

The third most frequently cited barrier to guideline adherence was the need to undertake a calculation to properly assess the severity CAP. This was reported to be a potential barrier by over half (54.3%) of senior doctors, but only around one in five responding junior doctors. Consistent with other international guidelines, TG comprises two sections regarding the management of patients with suspected CAP. The first part covers the assessment of CAP severity and this is a precursor to the second part, the selection of an empirical antibiotic regimen, based on the severity score. A number of severity scoring tools have been recommended by different CAP guidelines, (182, 186), including the Pneumonia Severity Index (PSI), which was the recommended tool in the previous version of TG (TG13) (302). Whilst all severity tools require some form of calculation to be undertaken, PSI is particularly complex, as it needs almost 20 variables to be considered. Recognising this, a number of less complicated tools have been developed, such as CURB65, CORB and SMART-COP (224, 234, 235); the last two of these being those recommended by TG14. As discussed earlier, physicians may not be aware of the change of the guidelines with regard to severity tool, which might explain their perceptions regarding the barrier posed by the need for a more complex calculation.

An important consideration related to severity assessment criteria to inform appropriate use of antibiotics for CAP is the lack of uniformity across various clinical practice guidelines. For example, CAP guidelines developed by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) were issued more than six years ago and do not make drug specific recommendations for hospital inpatients, instead they refer to classes of antibiotics such as Beta-lactams or macrolides, which leave interpretation open to using many possibilities (182). In contrast, the British Thoracic Society (BTS) and the Australian Antibiotic Guidelines (TG) recommend specific antibiotic regimens instead of antibiotic groups (144, 186). Our survey indicated that almost one-quarter of respondents thought that existing of other guidelines that conflict with TG14 recommendations regarding CAP management might explain the poor concordance with TG14. These findings are supported by the high self-reported use of the CURB65 severity tool (55.4%), which although recommended in the BTS and IDSA/ATS guidelines (182, 186), was not recommended in either TG14 or the previous TG13.

The perception that staff were not expected to follow the guidelines is another barrier that was suggested as contributing to low rates of adherence to CAP guidelines. Although not directly related to antibiotic prescribing, research by Gurses *et al.* found that clinicians are highly likely to adhere to particular guidelines when they know this is the expectation and norm in their department (303). Since the initial prescribers of antibiotics would most likely be junior doctors, as discussed earlier, perceptions regarding any expectation to adhere to guidelines might be determined by the prescribing behaviour of senior doctors and supervisors (161). Accordingly, if the senior doctors and supervisors prescribe antibiotics according to guidelines, it may be more likely that junior doctors will follow their prescribing habits. Another possible explanation for this might be related to organisational factors. For example, in their study, Schouten *et al.* showed that organisational factors, such as unavailability of an

antibiotic, lack of time and delayed laboratory results were possible barriers to optimal treatment of CAP (157). Given that most of the severity assessment tools require one or more laboratory tests, delays in obtaining these results might lead to none or inappropriate utilisation of the recommended tools to assess the CAP severity, which could lead selection of an inappropriate antibiotic regimen.

In this study, we also aimed to ascertain physicians' knowledge regarding the reasons why routine use of ceftriaxone for CAP is discouraged. Approximately three-quarters of the respondents thought that most cases were not severe and penicillin would give the same results as ceftriaxone. These findings suggest that physicians are aware of the severity profile of patients presenting with CAP that we reported in the baseline study, where the majority of CAP cases were non-severe. Additionally, most of the responders thought that one of the main reasons for not prescribing ceftriaxone for the majority of patients with CAP is due to the relationship of increased ceftriaxone usage and the emergence of multi-drug resistance microorganism. In one Swedish qualitative study, which was conducted to ascertain physicians' perceptions of antibiotic resistance in one hospital, it was shown that despite the high awareness of microorganism resistance, this awareness was less likely to influence prescribing decisions (304). The findings from our study suggested that most responders were aware that most of the CAP cases are not severe and penicillin-based therapy would be as effective as ceftriaxone. However, this was not reflected in practice where patients with non-severe CAP were frequently initiated on ceftriaxone-based therapy. These findings suggest that there might be other factors influencing the use of ceftriaxone for patients with non-severe CAP when it is not indicated. A qualitative study looking at barriers to CAP guideline adherence in three Dutch hospitals found that uncertainty about the suspected pathogen and lack of agreement with guidelines were common reasons for preferring broad-spectrum empirical antibiotic regimens. (157). Therefore, future research should concentrate on the

potential factors that could influence the use of ceftriaxone for patients with non-severe CAP at the RHH, taking into account that the vast majority of patients received their initial antibiotic regimens, including ceftriaxone, in the ED.

3.5. Limitations

There are limitations to this study that should be acknowledged. Firstly, this study was conducted in a single hospital; therefore, the results may not be generalisable to other institutions. Nevertheless, the aim of this study was to identify the potential barriers at this specific hospital (the target of our intervention) in order to tailor an intervention to overcome these barriers. Secondly, the findings were based on the respondents' thoughts about other doctors' poor adherence to TG14 CAP guidelines, not the respondents' assessment of the barriers affecting their own adherence. However, it has been shown that self-reported behaviour might not reflect the actual practices of surveyed physicians (305). Therefore, this method was used to overcome the possible bias that might arise if the physicians were asked directly about their adherence to guidelines. The response rate was relatively low. This might be due to physicians who have limited recent experience with CAP being reluctant to participate in the study. It is acknowledged that investigation into barriers to clinicians' concordance to guidelines using the quantitative approach is limited in its scope; this provided little room to explore barriers beyond those pre-determined as important by the researchers. Finally, demographics such as gender, age, and place of basic clinical training were not examined, and such factors may have influenced doctors' perceptions about adherence to guidelines, both generally and in terms of the TG14 recommendations for CAP in particular.

3.6. Conclusion

This study set out to determine potential barriers that might hinder doctors at the RHH from adhering to TG14 recommendations for CAP management. A variety of potential barriers to guidelines adherence was identified; the most frequently cited being the influence of senior doctors. On this basis, it is likely that the success of any intervention to improve CAP management at the RHH will be increased if this potential barrier is addressed. One way to do this would be to ensure involvement of senior medical staff in the development and implementation of guidelines at a local level.

Chapter 4. Factors influencing empirical ceftriaxone use in Community Acquired Pneumonia: emergency physicians' perspectives

4.1. Introduction

The results from the survey study (Chapter 3) showed that despite a low level of concordance with the TG14 in treating CAP at the studied hospital (Chapter 2), the majority of doctors surveyed reported familiarity and agreement with the recommendations of TG14. Moreover, as observed in the baseline audit (Chapter 2) few doctors reported the use of severity assessment tools to stratify patients into mild, moderate and severe categories of CAP. As the severity assessment is the very first step in guideline concordant care of CAP, identifying the limitations surrounding the use of severity assessments tools at the studied hospital was recognised as important.

A common observation from studies investigating physicians' concordance with CAP guidelines is that ceftriaxone, a broad-spectrum cephalosporin, is often prescribed outside guideline recommended indications (168). The baseline audit study at the RHH and NWRH (Chapter 2) also found the use the use of ceftriaxone was excessive and non-concordant to TG14. It is becoming increasingly recognised that there are significant adverse consequences associated with the use of broad-spectrum antibiotics (306, 307). Bloodstream infections caused by vancomycin resistant enterococci (VRE) are one of the life-threatening nosocomial infections that have been linked with the use of ceftriaxone (306). Furthermore, high levels of ceftriaxone use have also been associated with an increased incidence of CDI (307).

Given the fact that EDs are the first point of contact for most patients with CAP, an investigation to explore the factors limiting ED doctors' use of severity assessment tools and over-use of ceftriaxone within this care setting can inform the development of interventions to

improve CAP management. However, given the limitations of quantitative studies in this field, it was recognised that a better understanding of the issues would be gained by undertaking qualitative research. A qualitative study was therefore designed, with the following aims:

- To explore the emergency doctors views about the management of CAP in the ED setting.
- To specifically explore what factors influence the prescribing of ceftriaxone for CAP by ED physicians.

4.2. Methods

4.2.1. Participants and setting

This study was conducted in the ED of the Royal Hobart Hospital (RHH). All 40 doctors employed in the RHH ED at the time of the study were invited to participate in the study, through a mailed invitation letter and an information sheet containing further details of the research. Those doctors who signed and returned the consent form were then contacted to arrange a place and time for the interview. A store voucher to the value of 50 dollars was given to participants at the end of the interview in recognition of their time.

4.2.2. Data collection

One to one semi-structured interviews were conducted with participants. This method was chosen to enable ED doctors, especially junior staff, to speak openly about their practice regarding the management of CAP without fear of being criticised, and to enable them to discuss the issues they felt were important. The following questions were used to initiate and sustain discussion surrounding empiric management of CAP and the reasons for using ceftriaxone in CAP. Additional questions were raised based on each participant's answers to these initial questions (Appendix C).

The four initiating questions were:

- What are your thoughts on the empirical antibiotic management for patients presenting with CAP?
- What source(s) of information do you often rely on when making decisions about CAP treatment?
- What experiences do you feel have particularly influenced your prescribing practices in CAP?
- What leads you to prescribe ceftriaxone for patients presenting with CAP?

4.2.3. Data analysis

The interviews were conducted, recorded and transcribed verbatim by the student researcher (primary investigator; PI) and then analysed by using framework analysis (FA). FA is increasingly used in healthcare research due to its simplicity and the ability to provide direct link between conclusions and original qualitative data (308-311). FA was chosen for the present research as it also provides easy accessibility to the qualitative data for other researchers allowing them to review conclusions made by the original researcher. FA provides a systematic and rigorous process to manage qualitative data. It includes five distinct stages that result in the development of theme-based or case-based analysis, which can then lead to production of a chart which can be read by either cases or themes (311). FA includes five distinct stages:

1. Familiarisation
2. Identifying a thematic framework
3. Indexing and charting
4. Summarising and charting
5. Synthesising data by mapping and interpreting

4.2.4. Ethical consideration and approval

Participants provided signed consent prior to the interviews and were assured that any information provided would be treated confidentially. The student researcher interviewed the participants and was previously unknown to the interviewees. Ethical approval for the study was provided by the Human Research Ethics Committee (Tasmania) Network [Ref no: H00124809].

4.3. Results

Eight doctors responded to the invitation to participate in this study. Table **4.1** summarises the participants' characteristics. In the quotes reproduced below, the numbers represent the participants' order (i.e. P1 was the first participant interviewed and P8 was the last) and the subsequent letters represent seniority - consultant (C), registrar (G), or resident (R). This section will first describe the application of FA to the data obtained through interviews followed by the presentation of themes arising from the data.

Table 4.1: Participants' characteristics

Participants' number	Professional seniority	CAP cases/month	Part/full time in ED
P1	Consultant	6-12	Full time
P2	Registrar	6-12	Full time
P3	Resident	10	Full time
P4	Consultant	4	Part time
P5	Registrar	10	Full time
P6	Resident	5	Full time
P7	Registrar	10-15	Full time
P8	Registrar	1-2	Part time

4.3.1. Application of FA

Familiarisation

The main purpose of this stage was to become familiar with all transcripts in detail before developing any themes. To ensure immersion into all details of the data, the PI undertook all the interviews, transcribed the data, and studied all the data independently. Becoming aware of the main recurring themes was the main advantage of this stage. This was

facilitated by the small sample size (8 participants) and each interview lasted only 10 to 15 minutes.

Furthermore, notes were taken after each interview to enable the PI to record their immediate thoughts and emerging issues. These notes were utilised to enhance questioning in the subsequent interviews as well as to assess in developing themes in the next stage. All the data were analysed by the PI, while three random transcript samples were analysed by expert qualitative research analysts to ensure consistency and rigour.

Identifying a thematic framework

At this stage, repeated themes were identified from the familiarisation stage, and a chart was developed using the qualitative data software program NVivo., After familiarisation, the PI recognised emerging themes. The PI used the field notes that were taken during the familiarisation stage for guidance. This stage ensured that the original research questions were fully addressed. The main two questions were "what is the participant's strategy to manage patients with CAP in ED?" and "what might lead them to prescribe ceftriaxone in this case?". These themes were discussed with a group of three, one of whom had qualitative research experience at the university.

Indexing

Based on the previous stage, the thematic framework was applied back to the original data and field notes. The data were indexed under themes that were developed in the previous stage, where the themes were annotated on the relevant text in the transcripts. This strategy enabled the PI to become even more familiar with the data, so that the themes could be refined to become clearer and more accurate. More immersion in this stage would ensure that key themes are not overlapped, and the data only fitted one theme and were not repeated in another theme.

Summarising and charting

The main purpose of this stage is to briefly summarise what was said by participants and arranging these in a chart organised by themes. The same key word/s that the participants used was used in summarisation. A line numbering function in Microsoft Word was utilised to make it easy to retrieve the original data and the number of the page and line were written at the end of each summary. This approach provided a clear audit for the PI and other investigators and charting in this way would provide clarity of where the data came from.

Mapping and interpreting

The final themes were reviewed against the original transcripts, notes and the digital records by a qualitative research expert. Refinement of the themes was made accordingly. The charts and summaries were checked and reviewed against the themes and original data for any changes that were also needed. The final theme framework was agreed with the research group. Constant refinement of themes and returning to the original data leads to the development of a conceptual framework (312). Furthermore, at this stage the transparency produced by returning to the original data enhances rigour (311).

4.3.2. Emergent themes

Five main themes emerged regarding the factors that influence decisions to prescribe ceftriaxone for patients with CAP:

- Clinical intuition vs. structured evaluation of severity
- Clinical uncertainty
- Prior experience
- Source of guidance
- Prescribing etiquette.

Clinical intuition vs. structural evaluation of severity

All participants mentioned that they would use ceftriaxone in cases of severe CAP. However, participants mentioned different methods to identify patients with severe CAP. Although most interviewees were aware that using a severity assessment tool is recommended, only some of the participants actually used such a tool, and fewer used one of the severity tools specifically recommended by TG14, i.e. SMART-COP or CORB.

> *"It is quite easy really, in the absence of guiding from microbiology, it's a risk stratification based on the severity score. I would use the Therapeutic Guidelines, really. For empirical clinical management, [I would prescribe antibiotic regimen] based on the severity scores such as the CORB and SMARTCOP (P5 G)".*

Some of the doctors who used a severity assessment tool, used an alternative such as PSI or CURB65, either due to familiarity and/or because that was what they had been taught to use.

> *"The one that springs to mind is CURB65 because it's the one I know. Other ones I can't remember. That [CURB65] is just the one I've learned (P2 G)."*

The other participants mentioned that they relied solely on their clinical judgment to assess the severity of CAP.

> *"Most of it is the clinical picture of the patient. You see patients have difficulty breathing, short of breath, can't really speak, … are not stable, lower blood pressure, respiratory rate is elevated… .all of these things make you say OK this patient is not fine (P3 R)."*

Several reasons were stated regarding why CAP severity scores are not routinely used. The reasons included experience, education, and the changes in the recommended scoring system.

> *"I am aware of a quite a number of scores and systems one could use... But I guess that as one goes through your career, sometimes just through your own judgment and knowing about few key things can kind of get a sense of that yourself (P4 C)."*

"I know there are [severity tools], but they didn't teach us at med [medical] school. Like there is this SMART-COP and things like that. But in ED I haven't necessarily been encouraged to use that on the front line. I just go by your kind of gut feeling (P8 G)."

"In the past, they use PSI score, but this now has disappeared. I can't find it in TG anymore. So I just generally go by the clinical picture (P7 G)."

Some participants mentioned that in those cases of CAP likely to be admitted as an in-patient, the severity warrants ceftriaxone-based therapy.

"for empirical, it is normally ceftriaxone or some other 3rd generation cephalosporin 1 gram or 2 grams IV daily plus macrolide (azithromycin)… that's normally for patients who are for admission (P3 R)."

It was frequently mentioned that the perception of severity is often influenced by the presence of co-existing diseases, as one interviewee said:

"A lot of patients have pneumonia which is only severe because of the comorbidity…the number of diabetic, ischemic heart disease, heart failure, …much more complicated patients than perhaps they were 20 years ago (P1 C)."

Clinical Uncertainty

Clinical uncertainty was a common theme that all participants believed could be a major factor explaining prescription of ceftriaxone outside of guideline recommendations. An example of this was where the prescriber was unable to identify the source of infection or a suspicion that there may be multiple sources of infection.

"It is not clear in the first day what is really going on with this patient… it is not that clear it is the pneumonia causing the patient's presentation. For the inpatient team, it is different story, but for ED you don't really know what the patient has, you are the first line of the treatment (P7 G)."

"If I was not entirely sure about the source, if there is concomitant UTI, I think ceftriaxone gives good broad spectrum coverage (P6 R)."

Some participants mentioned that the time limitations in the ED could be one reason to prescribe ceftriaxone even if they are not sure about the diagnosis.

"I think in the emergency setting sometimes because people really in a hurry, they can't really decide what to do, and they want to push the patients as soon as possible and let the patient go out from the ED and decide if the patient should go home or should be admitted. Actually, that's the nature of the ED, to decide as quickly as you can. Sometimes, I feel that's the reason why we prescribe ceftriaxone in ED (P3 R)."

Prior experience

It was frequently mentioned that the broad spectrum and generally good safety profile of ceftriaxone might make it attractive to be used in the ED as one interviewee put it:

"I guess because ceftriaxone is a fire and forget weapon. Give it then the patient gets better. ..and there are very rare major side effects acutely. I guess people think that they cover their back by giving ceftriaxone (P7 G)."

Some participants stated that ceftriaxone leads to less treatment failure than may be seen with other agents recommended for non-severe CAP. Talking about this issue, an interviewee said:

"Just from my experience it [ceftriaxone] always works. I haven't seen a lot of treatment failure with ceftriaxone. On the other hand, benzylpenicillin, I've seen several patients not getting better with that (P7 G)."

Source of guidance

Participants used different resources to guide their choice of antibiotic therapy, including ceftriaxone, for patients with CAP.

All participants stated that they utilised Therapeutic Guidelines (TG) to inform empiric treatment of CAP patients in the ED.

"I normally follow the TG [Therapeutic Guidelines: Antibiotics]. You need to make the decision whether to admit the patient or send the patient home. I found this quite helpful (P7 G)."

However, when asked about their thoughts regarding empirical management of CAP, some participants reported occasional use of antibiotic regimens that were not in accordance with TG.

"I feel that I would rather give people [IV] amoxycillin rather than straightforward benzylpenicillin because I think it is slightly broader…I have never prescribed ceftriaxone for most people with pneumonia…sometimes I think I tend to give old smokers oral Augmentin [amoxycillin/clavulanic acid] when probably it is inappropriate, but they've been on it before and it's got extended cover and it probably has less resistance (P1 C)."

Some participants also utilised international references to seek guidance regarding treatment decisions.

"In the hospital I usually use UPTODATE, which is an American site. We normally have it in the computers at the hospital. ..I know there are some other sites and applications would help you as well. I really feel comfortable with UPTODATE (P3 R)."

Prescribing etiquette

Discussion with colleagues regarding the use of ceftriaxone for CAP ranged from extremely rare with consultant participants, extremely rare to sometimes with registrars, to most of the time and always with residents.

"No, not for ceftriaxone…the only time that I ask for sort of guidance are for people with sensitivities to antibiotics or when it is an unusual infection, significantly immunocompromised patient, then I might talk to ID about what would they like to give…invariably, it is not ceftriaxone (P1 C)."

"I sometimes consult my colleagues, but I feel comfortable if I feel the patient is sick enough; I just give it. Sometimes I consult with my consultant whether they are happy with that plan. But in general if it is a sick patient, I don't have too much doubt in giving them unless they are allergic and need to solve other problem (P7 G)."

"Definitely I use the consultants because I'm a junior doctor... Because I was a junior I used to discuss it [ceftriaxone]; for example, before I give it to the patient (P3 R)."

All consultants and most registrars thought that the inappropriate prescribing of ceftriaxone might originate with junior doctors.

"It is difficult… particularly if people [juniors] have been working in these areas with septic patients in intensive care and oncology, and they have a rotation to ED, then they are going to feel that's appropriate to use those antibiotics for the sicker patients, where the sickness is not necessarily related to the… you know the correlate between antibiotics and unwellness (P1 C)."

It was also mentioned that there is less restriction on prescribing ceftriaxone in the ED and most of the time senior doctors do not object when they have been asked. Participants also reported that the general principle of 'do no harm' applies to the use of ceftriaxone due to its safety.

> *"I really sometimes think that we just give ceftriaxone to patients unnecessarily. And actually we did give those patients ceftriaxone unnecessarily many times. I think you can see it with all doctors as a resident, as a consultant, as everyone. ..I always think that there is feeling in all of doctors that antibiotics won't do anything [harmful] "one or two doses of ceftriaxone won't kill anyone (P3 R)."*

4.4. Discussion

Following the work described in the previous chapter to identify barriers that hinder doctors from adhering to recommendations, this qualitative study was designed to determine factors that influence ED doctors to prescribe ceftriaxone outside the TG14 recommendations. Five broad themes emerged from the analysis that could describe and explain some of our findings from the baseline audit (Chapter 2) and survey study (Chapter 3).

4.4.1. Assessment of CAP severity

There was general agreement that ceftriaxone is required for patients with severe CAP. However, despite this, participants used different methods to assess CAP severity. For example, half of the participants reported not using any severity scoring tool despite an awareness of them. Those participants reported the use of non-objective measure of pneumonia severity such as need for admission, clinical judgment and co-exiting diseases. Subsequent to this self-perceived subjective assessment of pneumonia severity, ceftriaxone was being used for patients who would not have received it if treatment decisions were based on objective assessment of severity.

Some of these findings were similar to previous published studies. For example, a qualitative study looking at reasons behind non-adherence to guideline recommendations among Dutch general practitioners found a perception that some guideline recommendations are not applicable to some groups of patients, such as those with a co-morbidity (159). A systematic review looking at factors influencing adherence to clinical guidelines among health care providers showed that patients' characteristics, such as co-morbidity, increase the chance that recommendations are not followed (313). The need for admission was also reported as an indicator of CAP severity and consequently justification for using ceftriaxone. However, according to the TG14, some patients who are admitted may have moderate CAP and

ceftriaxone is not recommended unless the patient is allergic to penicillin. It should also be acknowledged that in some cases, the decision to admit for treatment may be related to social factors, rather than the severity of CAP as such (144). Reliance on clinical judgment to identify patients with severe CAP is another theme that was noted in this study. It has been reported that ED physicians are more likely to overestimate the severity of CAP, which leads to unnecessary hospitalisation and use of inappropriately broad-spectrum antibiotic therapy (275). It has also been reported that when ED prescribers deviate from guidelines, there would be a tendency to use broader spectrum antibiotics than those recommended by the guidelines (314). Furthermore, in one Australian study, it was shown that most of the empiric ceftriaxone therapy initiated in the ED was subsequently altered after admission (168). It can perhaps be assumed that ceftriaxone usage was, in such cases, inappropriate in the first place.

Even with those participants who reported use of a tool to assess CAP severity, there was inconsistency in their chosen tool. This is an important point as the use of different tools, such as PSI or CURB65, for an individual patient may result in a different severity score. Various severity tools have been proposed to assist doctors in making decisions regarding the empirical management of CAP, yet, there is no agreement about the best assessment severity tool (221). Therefore, national and international guidelines often recommend one or two of the validated assessment tools to assess the severity of CAP with justification based on experts opinion (144, 182, 186). The non-agreement about the best tool to assess the severity might lead doctors to gravitate towards the tool they are most familiar with and this was mentioned by some participants. Uncertainty

Uncertainty regarding the diagnosis appears to be an important influence on prescribing of ceftriaxone in the ED and this might be due to the nature of ED, where doctors have limited time to make a decision. Uncertainty over the source of infection or the effectiveness of narrower spectrum antibiotics in a specific case scenario could lead to the prescribing of a

broader-spectrum antibiotics “to be on the safe side” (304, 315). As an example, a doctor might prescribe ceftriaxone empirically if it is not clear whether a patient has UTI or CAP, and since ceftriaxone covers both *E.coli*, the pathogen most frequently identified as causing UTI, as well as *S.pneumoniae*, the most common pathogen in CAP; and this may be reasonable (144). The high pressure ED environment might encourage use of ceftriaxone for patients with suspected CAP, as one of the participants reported. In their studies, Fee *et al.* and Pines *et al.* found that there was an association between increasing volume of patients in the ED and delayed antibiotic administration for patients with CAP (316, 317). Efforts to reduce the overcrowding in EDs by introducing the 4-hour rule, that is, the decision to admit or discharge a patient from the ED should be taken within four hours of presentation to the ED (318), might have added to pressure on doctors at the study site to prescribe ceftriaxone. Uncertainty and difficulty in confirming a diagnosis of CAP upon admission, particularly for patients with a clear chest X-ray, was also reported as one of the issues that might lead to inappropriate management (253).

4.4.2. Experience with ceftriaxone

The interviewees frequently compared their experience with ceftriaxone and penicillins for the management of CAP, and it was always highlighting an advantage for ceftriaxone. Interviewees stated that a once daily dosing of ceftriaxone makes it attractive as a treatment option for patients with CAP. This advantage is not seen with other recommended antibiotics, particularly penicillins. For instance, benzylpenicillin is required to be administrated four times within 24 hours (144). With respect to clinical outcomes, there was a sense amongst interviewees that ceftriaxone, due to its broad-spectrum coverage, when compared to penicillin, has better clinical outcomes. As one of the participants mentioned, his own experience has led him to perceive patients are more likely to return to the ED a few days later with no improvement when penicillin-based therapy is prescribed. In their qualitative study of

barriers to CAP guideline adherence, Schouten *et al.* found that one of the reasons for not using penicillins for the management of CAP patients was doubts about the outcome with those narrow-spectrum antibiotics (157). This would suggest that the preference to prescribe ceftriaxone might be due to less confidence about penicillin-based therapy in some cases.

4.4.3. Influence of senior doctors

In common with other departments, the ED is staffed by doctors with varying levels of seniority and these may all be involved in the management of patients with CAP. The influence of senior doctors on prescribing practices of junior doctors has been demonstrated in several studies (163, 165, 315). According to Charani *et al.*, the prescribing of antibiotics is influenced by "prescribing etiquette"; which does not reflect any written rules, but acceptance of culture norms (163). By way of illustration, Charani *et al.* found that senior physicians generally considered themselves to be experts and relied on their personal experience in prescribing (163). Junior doctors, on the other hand, are influenced by the prescribing habits of their seniors. Therefore, the authors suggested that despite most interventions promoting prudent use of antimicrobials being directed at junior doctors, the practice of the senior doctors is the main determinant of their junior colleagues' prescribing (163). Hierarchies might play a role in influencing junior doctors' decisions about prescribing antibiotics (163), our study showed that junior doctors are more likely to make decisions about prescribing ceftriaxone, yet, they are likely to seek confirmation by consulting with their seniors. Interestingly, despite this finding from junior doctors, there was a sense amongst senior doctors that it was the junior doctors who were responsible for ceftriaxone prescribing outside guideline recommendations.

Other possible explanations for unnecessary prescribing of broad-spectrum antibiotics are worth exploring. Leake *et al.* identified several factors that might lead medical residents to prescribe broad-spectrum antibiotics unnecessarily. These factors included lack of awareness

of the possible serious adverse effects associated with prescribing such antibiotics and issues related to antimicrobial spectra (319). Another important finding in the present study is the influence of rotation on junior doctors' prescribing practice as mentioned by one interviewee. This might provide juniors with conflicting opinions with regard to antibiotic prescribing. A qualitative study looking at factors influencing antimicrobial prescribing among junior doctors in two UK hospitals found that health care culture was the main factor that influences the antimicrobial prescribing (320). Among these cultural aspects, it was identified that there can be a major variation between wards in the same hospital in terms of antimicrobial prescribing expectation and support, particularly with rotations which need rapid adjustment to the new rules.

4.4.4. Quantitative and qualitative studies: putting it all together

The results from this qualitative study will now be compared to the findings of the earlier quantitative study reported in Chapter 3. Firstly, in the preceding chapter, we found that senior doctors were the most commonly reported influence on prescribing. The qualitative study explored how this influence was likely to occur. Secondly, the results from the questionnaire indicated that different severity scoring systems were used. This also concurs with the findings from the qualitative study which showed that different severity scoring systems were used among ED doctors to identify severe CAP. Apart from the established objective tools, other methodologies were also used as an indicator for severity, such as clinical judgment, co-existing disease and need for admission. Thirdly, despite the high awareness of the relationship between use of ceftriaxone and emergence of multi-drug resistance, when doctors were asked about why this drug is not recommended for most CAP cases, none of them mentioned concerns about resistance as an influencing factor. This is consistent with other studies, which have reported that the desire to use a treatment with a high likelihood of curing the infection is the major driver at the time of prescribing (304, 315).

Finally, most of the survey respondents agreed with the statement that penicillin-based therapy would give the same results as ceftriaxone in most CAP cases. Nonetheless, some participants reported a lack of confidence in the effectiveness penicillin-based compared to ceftriaxone-based therapy, according to their own experience with the both regimens.

4.5. Limitations

A number of important limitations need to be considered. First, while prescribing of antibiotics in the RHH ED may be undertaken by any medical specialty, all participants in this qualitative study were ED-based prescribers. Therefore, the opinions of other staff who may have an indirect influence on ceftriaxone prescribing decisions in the ED were not recorded. However, the main aim of our study was to survey those first-line practitioners who initially assess patients in the ED. The sample size was also relatively small (8 physicians) which was a consequence of time pressures on ED staff; however, all the physicians who were interviewed were working in ED, and it has been shown that for a study with a high homogeneity level, as few as six interviews could be sufficient to reach saturation with meaningful themes and enable a meaningful interpretation (321). Finally, this study focused on the factors that influence use of ceftriaxone-based therapy for patients with CAP; the barriers hindering physicians from prescribing penicillin-based therapy received less attention. Nevertheless, one of the main purposes of antibiotic guideline development is to limit the emergence of resistance by limiting unnecessary use of broad-spectrum antibiotics, such as ceftriaxone; which is consistent with the targets of RHH antimicrobial stewardship team.

4.6. Conclusion

Our study identified a number of modifiable and non-modifiable factors influencing the prescribing of ceftriaxone in ED. Factors such as clinical uncertainty are difficult to modify, as the limited time a patient spends in the ED can be challenging to make a definitive diagnosis of CAP and its degree of severity. In contrast, factors relating to the source of prescribing guidance and professional etiquette can be addressed by establishing local CAP management guidelines and treatment pathways, with engagement from senior clinicians. The findings from the current study, together with the results from the preceding chapter provide an important insight into the barriers that hinder doctors from adhering to TG recommendations for the management of CAP. Addressing each of these factors would be pivotal to the success of any intervention designed to increase adherence to CAP guidelines and specifically reduce inappropriate prescribing of ceftriaxone in the ED.

Chapter 5. Snapshot of intervention strategies used to improve CAP management in Australian public hospital ED departments

5.1. Introduction

The Emergency Department is the site of care where most patients with CAP, are initially seen and empirically treated with antibiotics (317). However, it has been shown that broad-spectrum antibiotics, such as ceftriaxone, have been commonly prescribed inappropriately for ED patients with CAP (168). Therefore, the ED is likely to be an ideal target for interventions to improve CAP management.

Despite AMS activities being well-established in the in-patient setting, they have traditionally focused little attention on EDs in Australia. To help us identify appropriate strategies for our interventions, this study aimed to:

- Explore the general role of AMS in ED
- Explore the perception regarding effective strategies to improve the appropriate use of antibiotics for CAP patients in Australian EDs.

5.2. Methods

5.2.1. Setting and participant characteristics

An electronic link to a web-based questionnaire was circulated via email to the infectious diseases pharmacist group of the Society of Hospital Pharmacists of Australia (SHPA). The estimated number of pharmacists in this group was 150 at the time of the study in July 2013. Two e-mailed reminders were sent at one-week intervals.

5.2.2. Questionnaire and measurement

The questionnaire consisted of three main sections. The first included questions regarding hospital's characteristics including state, number of beds, and information about the status of AMS within the institution. The second section included questions regarding initiatives that have been made by the participants' hospital to improve antibiotic prescribing for CAP in the ED and the initiatives that were perceived as effective. In the final section, the participants were asked to briefly describe the overall role of the AMS program in their hospitals' EDs.

5.2.3. Data analysis

Chi-square tests were used to identify statistically significant differences between variables and the value of $p < 0.05$ was considered statistically significant. All the statistical tests were performed by using IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.

Approval from the Human Research Ethics Committee (Tasmania) network was granted prior to the conduct of the survey [approval no.: H0013156].

5.3. Results

5.3.1. Response rate hospital characteristics

Of the study population, 41 (27.3%) participants completed the questionnaire. Hospitals characteristics are described in Table 5.1. All respondents worked in public hospitals.

Table 5.1: Hospital characteristics.

State/ Territory	Queensland (QLD)	10
	Victoria (VIC)	9
	New South Wales (NSW)	9
	South Australia (SA)	5
	Western Australia (WA)	5
	Tasmania (TAS)	2
	Australian Capital Territory (ACT)	1
Hospital's capacity	100 – 300 beds	9 (22%)
	301 – 500 beds	16 (39%)
	More than 500 beds	16 (39%)
Year of establishment of AMS program	Before 2011 (inclusive)	13 (31.7%)
	After 2011	24 (58.5%)
	No AMS program	4 (9.8%)
Periodically monitor antibiotic usage in ED		21 (51.2%)
Utilisation of CAP guidelines	TG14	18 (43.9%)
	Local guidelines	22 (53.6%)
	No guidelines recommended	1 (2.4%)

5.3.2. Process of care for the management of CAP in ED

A number of different approaches were in place to improve the prescribing of antibiotics for patients with CAP (Figure **5.1**). Academic detailing was the least common strategy that respondents reported as using to enhance CAP management (7.3%).

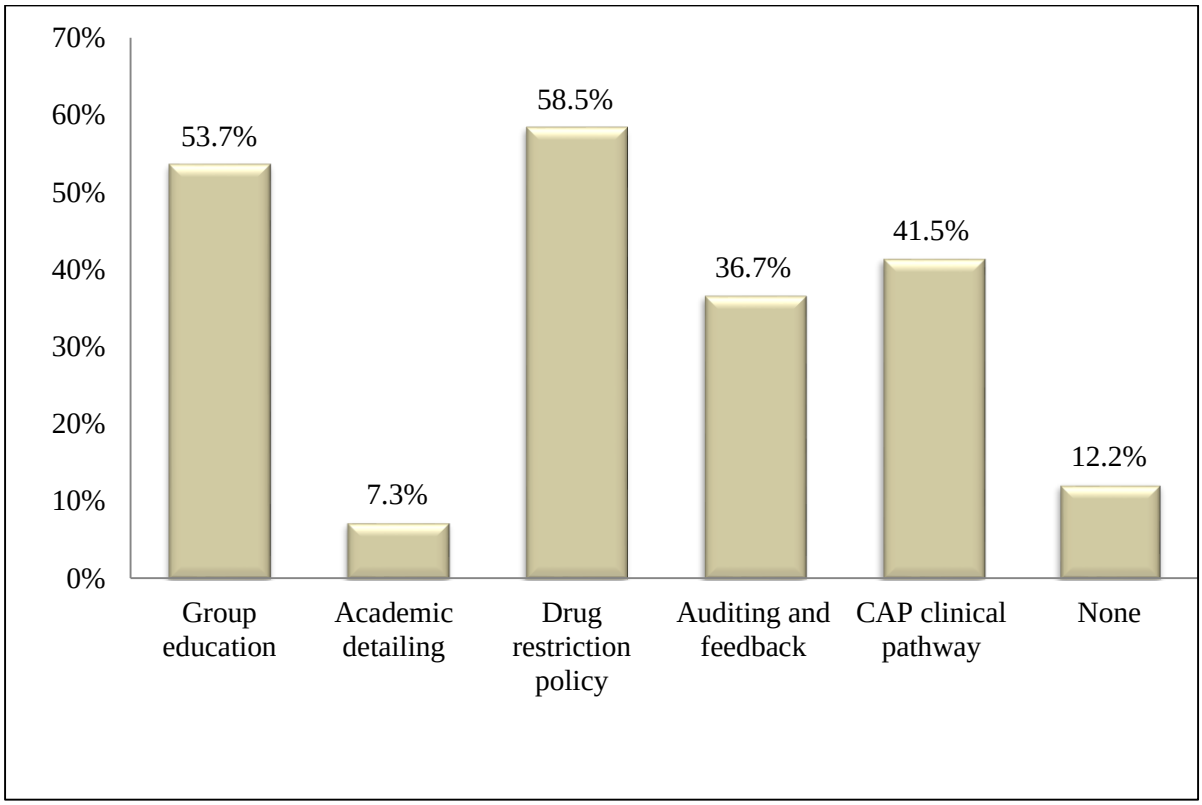


Figure 5.1: Strategies that had been used to improve antibiotics use for CAP management in ED.

When the participants were asked about their perception of the effectiveness of the strategies that had been employed in their hospital, there was no clear preference for individual selected strategies (Figure **5.2**).

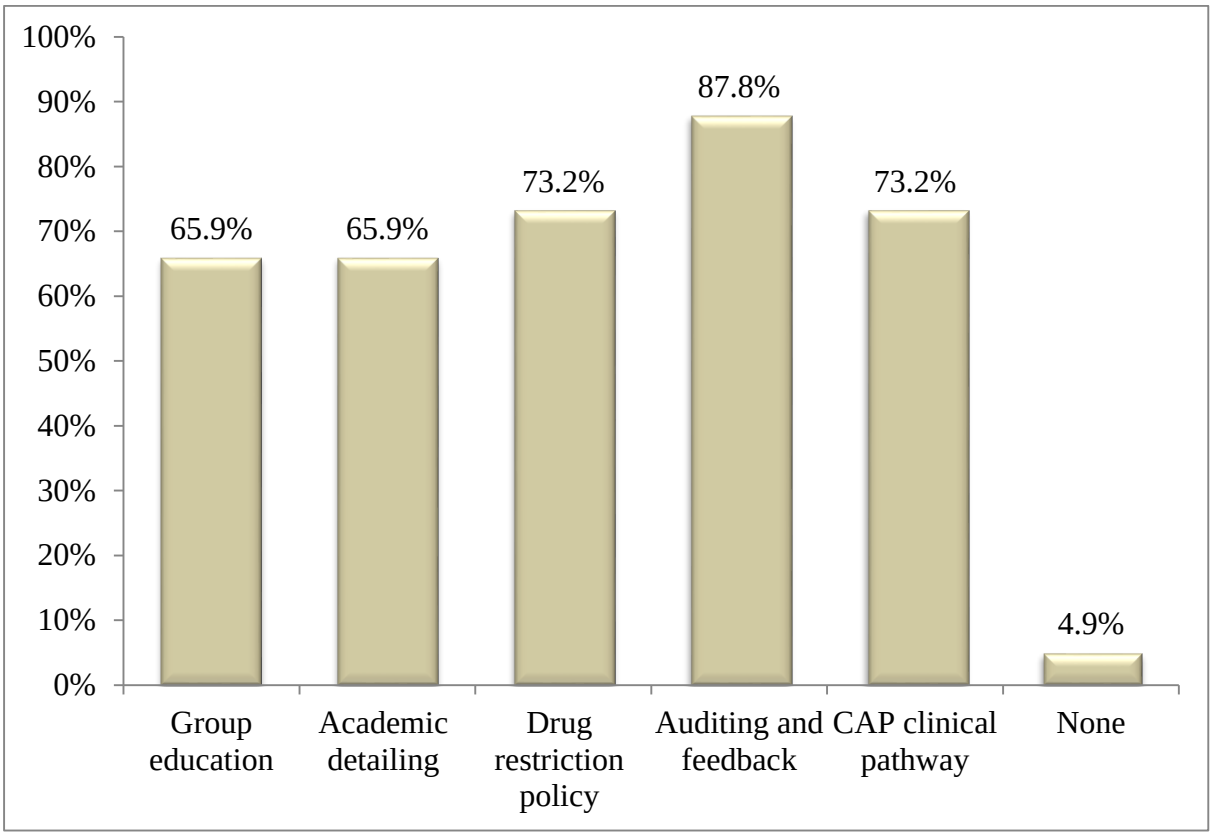


Figure 5.2: Strategies that had been perceived as effective to improve use of antibiotics for the management of CAP in ED.

Participants reported CAP clinical pathways (34.1%) followed by academic detailing (24.4%) and auditing and feedback (17.1%) as the most effective strategies in improving the management of CAP at their hospitals. Surprisingly, only 1 participant reported that conducting group educational sessions was the most effective strategy (Figure **5.3**).

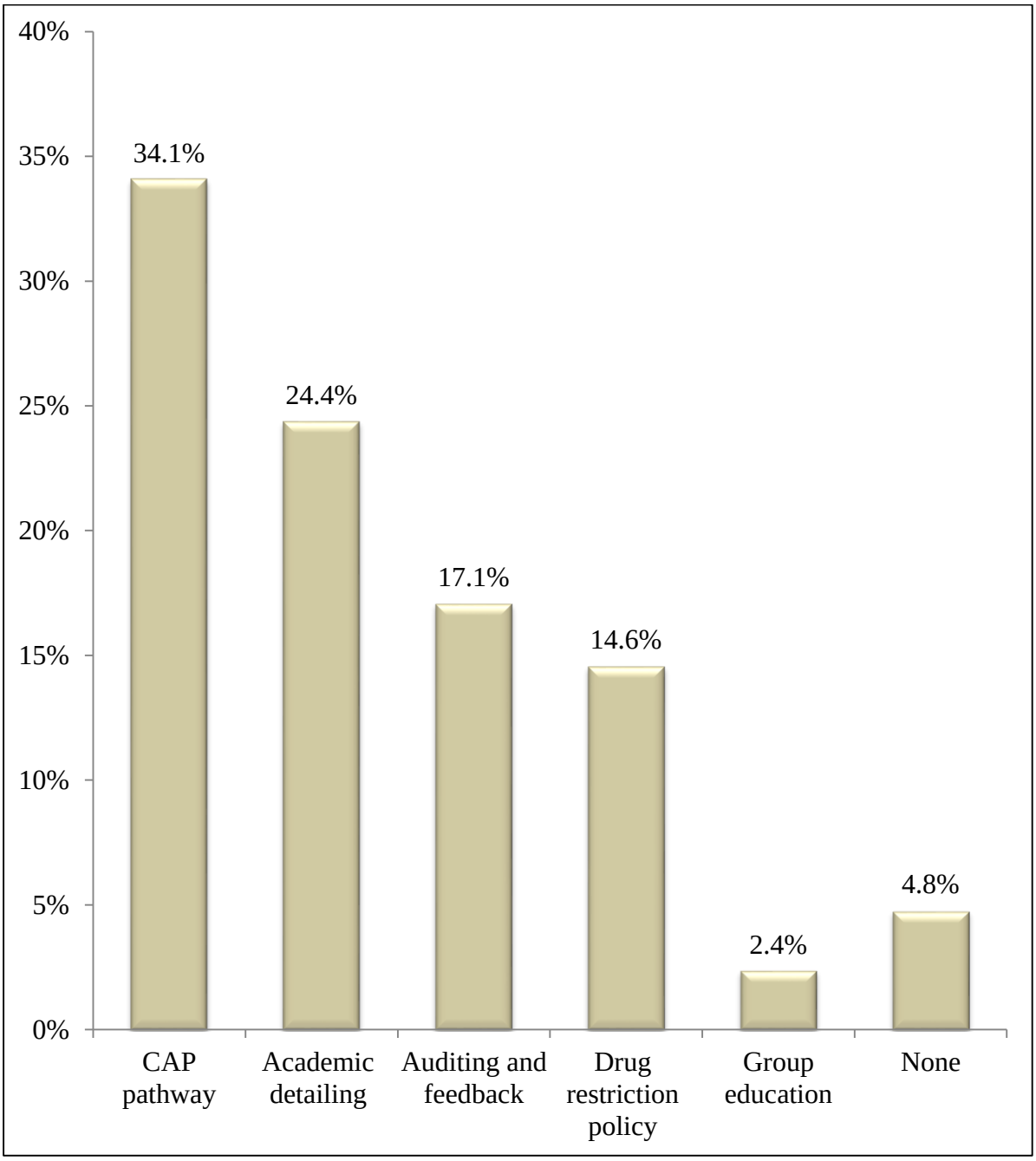


Figure 5.3: Strategies perceived as the most effective strategy for better use of antibiotics for patients with CAP in ED.

Those who reported the presence of AMS in their hospitals were invited to describe the extent of AMS activity in the ED. Of the 37 participants who reported their hospital had an AMS, 24 answered this optional question. The reported roles of AMS in ED are listed in Table 5.2. Nine respondents indicated no current AMS activity in the ED due to the program being new and the focus being on in-patient wards.

Table 5.2: Roles of AMS in the ED setting (n= 15).

Role of AMS program	Frequency [a]
Development of local guidelines	4
Monitoring local antibiotic susceptibility	1
Restriction policy	4
ED pharmacist liaising with ID	2
Regular education by ID	5
Involvement of ED senior in AMS hospital program	4
Audit and feedback	6
Clinical decision support system (CDSS)	2
ID physician rounds in ED	1

[a] The cumulative frequency does not add up to 15 since more than one strategy might have been utilised.

The presence of local CAP guidelines was significantly more likely in hospitals where AMS was in place in 2011 or earlier (84.2% vs 37.5%; $p = 0.014$). However, there was no difference in the periodic monitoring of antibiotic usage in ED between those hospitals who had implemented AMS in their hospitals before and after 2011 (69.2% vs 47.6%; $p = 0.3$).

The vast majority of participants reported that ED staff required more education to increase adoption of CAP guidelines (63.4% strongly agree, and 29.3% agree).

5.4. Discussion

The main objective of this study was to identify strategies that have been used and perceived as successful for the management of CAP among EDs in Australian hospitals. The results of this study showed the hospitals have used more than one strategy to enhance antibiotic prescribing in ED for CAP. However, most of the respondents considered the most single effective strategy to be the use of CAP clinical pathways.

Our study indicates that multifaceted strategies are the most utilised and seemingly most effective methods to improve the empirical management of CAP within ED in Australian public hospitals. Similarly, another Australian study showed that the use of a variety of strategies to improve antibiotic usage was a common phenomenon (138). Several meta-analyses related to the effect of single interventions in changing physicians' decision-making process found limited improvement in changing prescribing behaviours (322-327). Multifaceted strategies have been demonstrated as an efficient approach that can effectively improve care, as well as clinical outcomes (117, 128, 146, 154, 170, 328-331). According to Grimshaw *et al.*, multifaceted and active interventions are more likely to work in changing physicians' prescribing behaviour than passive dissemination or single interventions (332). As a successful example of this type of approach, Wong-Beringer *et al.*. found a 30% decrease in empirical prescribing of broad-spectrum fluoroquinolone antibiotics, when multifaceted interventions were utilised (126).

To ensure effective and sustained compliance with antibiotic guidelines both systematic and educational initiatives should be implemented. ACSQHC provides an example of an essential systematic change, endorsement of local guidelines that are based on the latest Australian national *Therapeutic Guidelines*, as one of the fundamental strategies for successful AMS (117). Development of ED-specific guidelines, or clinical pathways, accompanied by education could be a powerful strategy to encourage adoption of CAP guidelines in ED (333).

CAP clinical pathways were perceived as the most single effective strategy that could improve adherence with guidelines in ED. Using clinical pathways might be particularly effective for the ED where a quick decision is required to admit or discharge patients (333). A clinical pathway can help expedite the process with appropriate decisions regarding assessment, admission and antibiotic/s selection.

The study also indicated that academic detailing was perceived as the second most effective strategy. In a Cochrane review relating to the effect of academic detailing on changing clinical practice including 69 studies, the authors concluded that using academic detailing approach have a positive but small effects on prescribing behaviour (327). However, this strategy might be difficult to conduct in a busy clinical environment, such as ED. In a qualitative study to get participants' thought about the academic detailing strategy that were used to improve compliance with CAP guideline's recommendations in Australian EDs, it was argued that this strategy was time-consuming for both the providers and for ED doctors (277). This may explain why academic detailing was the least reported approach by participants in our study.

AMS plays a very important role in designing and implementing strategies to improve antibiotic prescribing in the in-patient and ED settings. This includes the development and promulgation of local guidelines. Respondents who reported the presence of AMS in their hospitals before 2011 were more likely to report the presence of local CAP guidelines. Almost 90% of participants in our study reported the presence AMS in their hospitals, but only one-third of them reported the AMS programs were officially implemented before 2012. This is consistent with a survey that was conducted in 80 Australian hospitals in 2008, where only 24% of the respondents, pharmacy department directors or their nominees, reported the presence of AMS program in their institutions (138). Moreover, when AMS programs are first introduced, the first priority is invariably for admitted patients, and newer AMS programs

might not have perceived roles in the ED. This theory is supported by the responses from nine participants with a new AMS program.

5.5. Limitations

The major limitation of this study is the relatively low response rate (27.3%). However, the aim of this study was to determine a snapshot of initiatives that have been performed in hospitals to improve the management of CAP in ED and is therefore unlikely to compromise the validity of the findings.

5.6. Conclusion

These findings suggest that, in general, non-specific multifaceted strategies are frequently performed to improve use of antibiotics for CAP management in Australian EDs. However, CAP clinical pathways were perceived to be the single most effective strategy. The evidence from this study suggests that a CAP clinical pathway should ideally be part of any intervention designed to improve CAP management in the ED. The findings from this chapter alongside the findings from the chapters, 2, 3 and 4, would be used to develop targeted interventions aimed at improving adherence to CAP guideline recommendations, including attempts to reduce inappropriate ceftriaxone prescribing and improve clinical outcomes.

Chapter 6. Interventions

6.1. Introduction

The findings reported in Chapter 2 provided clear evidence of sub-optimal adherence to TG14 for the empirical therapy of CAP in adults in two Tasmanian hospitals, with the widespread use of ceftriaxone for patients with non-severe CAP, a significant contributor to this issue. Similar findings have been reported in the national and international medical literature (220, 334, 335). Therefore, based on this evidence–practice gap, an intervention to change behaviour was designed, with the desired outcome being to improve adherence to guideline recommendations for empirical CAP management; which would consequently reduce the inappropriate use of ceftriaxone-based therapy for patients with non-severe CAP.

The vast majority of patients with CAP were diagnosed and accordingly prescribed their first dose of antibiotics while in the Emergency Department (ED). In the vast majority of cases, these clinical decisions were made by medical staff based in the ED; but in some cases doctors from medical admission teams were consulted and prescribed antibiotics for CAP patients in the ED (250). Consequently, ED medical staff were the main professional group to be targeted by the intervention, however, recognising the involvement of other medical teams in some cases, they were also exposed to our intervention.

To guide the choice and the design of the intervention, we identified the potential barriers that might hinder medical staff from adhering to national CAP guidelines for empirical therapy (Chapter 3). This was followed by a qualitative study involving prescribers in the ED at the RHH to gain an in-depth understanding of the factors that influence their prescribing of ceftriaxone for patients with suspected CAP (Chapter 4). In addition, the findings of Chapter 5 also highlighted some of the strategies that were considered by infectious disease pharmacists to be effective in improving the management of CAP.

Decisions regarding the most appropriate intervention strategies to improve adherence to CAP guidelines amongst RHH doctors was influenced by these collective findings, combined with the experience of the RHH Antimicrobial Stewardship (AMS) team.

It has been shown that interventions to improve clinical practice are more effective if the interventions are based on addressing existing barriers to best practice (336, 337). Multifaceted interventions to improve clinical practice appeared to be more effective than single interventions (338). Therefore a multifaceted intervention combining several strategies was designed to improve the physicians' concordance with CAP guidelines at the RHH.

The following section of this chapter will describe the components of the multifaceted intervention followed by a plan to evaluate the effectiveness this intervention in improving the physicians' concordance with CAP guidelines.

6.2. Components of the multifaceted intervention

Feedback on the findings of the baseline (Chapter 2), qualitative (Chapter 4) and survey studies (Chapter 3 and 5) was provided to a meeting of the RHH AMS committee. This committee has representation from several departments in the hospital which include, but are not limited to, respiratory, infectious disease, microbiology, pharmacy, and emergency departments. The rationale for presenting the findings to the committee was to facilitate discussion, seek comments and feedback on the possible initiatives that could be implemented to improve CAP management at the RHH. A number of initiatives were agreed upon as a result of this process and subsequently implemented as a part of the multifaceted intervention as shown in Table 6.1.

Table 6.1: Proposed initiatives based on the findings from the survey and interviews.

Proposed intervention design		Rationale
➢ **Development of local CAP guidelines (based closely on TG14)** ➢ **Involvement of hospital stakeholders in the local guidelines' development**		• To provide local ownership • To address perceptions that the organisation did not expect guideline adherence • To overcome the barrier regarding existence of other guidelines • To harness the support of senior doctors to be a positive influence • To overcome lack of awareness • To address inconsistency with regard to severity assessment • To unify the source of guidance
General Intervention	➢ **Education package (posters, lanyard cards, presentations, and group discussions)**	
ED focused interventions	➢ **Development of CAP clinical pathway in ED** ➢ **Monthly auditing and feedback**	

6.2.1. Local guidelines development

The process of developing a local CAP guideline was initiated through an initial meeting with the key stakeholders including representatives from Respiratory, Infectious Diseases, General Medicine and Emergency Departments. Following this, further meetings and correspondence occurred to refine the document and this resulted in the production of a final draft version. This was circulated via email to gain final approval from stakeholders before proceeding to the relevant hospital committees for endorsement of the guideline, printing of hard copy resources and publication on the hospital intranet.

The local CAP guidelines included recommendations regarding diagnostic strategies, admission decisions, severity assessments and antibiotic regimens. With regards to the empirical management, minor changes to the TG14 recommendations, to take account of the opinion of the hospitals' medical and emergency departments, were made (Table 6.2).

Table 6.2: Antibiotic recommendations for the management of adult patients with CAP at the RHH.

Criterion	First line therapy	Mild penicillin allergy	Severe penicillin allergy
Mild CORB = 0 *Stable comorbidities*	**Amoxycillin** 1 gram orally 8-hourly (OR if atypical pathogens are suspected treat as mild penicillin allergy)	**Doxycycline** 200 mg orally stat then 100 mg 12-hourly (OR if Doxycycline not tolerated then use Clarithromycin 500 mg orally 12-hourly)	
Moderate CORB = 1 *(Assessment of co-morbidities as may require ICU assessment)*	**Benzylpenicillin** 1.2 gram IV 6-hourly **AND** **Doxycycline** 200 mg orally stat then 100 mg orally 12-hourly (OR if Doxycycline not tolerated then use Clarithromycin 500 mg orally 12-hourly)	**Ceftriaxone** 1 gram IV daily **AND** **Doxycycline** 200 mg orally stat then 100 mg orally 12 –hourly (OR if Doxycycline not tolerated then use Clarithromycin 500 mg orally 12-hourly)	**Moxifloxacin** 400 mg orally daily
Severe CORB = 2 or more *(Consider ICU consultation)*	**Ceftriaxone** 1 gram IV daily **AND** **Azithromycin** 500 mg IV daily	**Ceftriaxone** 1 gram IV daily **AND** **Azithromycin** 500 mg IV daily	**Moxifloxacin** 400 mg IV or orally daily **AND** **Azithromycin** 500 mg IV daily

With regard to the antibiotic regimen recommendations, the dose of doxycycline for patients with moderate CAP was recommended to be 200 mg initially instead of starting with 100 mg as per TG14. The rationale behind this decision was to make the dose consistent with what is recommended in mild CAP so reduce the risk of confusion. The same justification was applied to clarithromycin, where a dose of 500 mg was recommended for patients with mild CAP, rather than the 250mg as per TG14. Moreover, despite the fact that TG14 includes an option to use aminoglycoside-based therapy for patients with severe CAP, the AMS team preferred to only retain the ceftriaxone-based option. The rationale for this was that most patients in the baseline study were over 65 years, a group of patients in whom renal impairment is more prevalent, which increases the risk of harm with aminoglycoside therapy.

Furthermore, simplification of the guideline recommendations to provide doctors with fewer options at each level of CAP severity was deemed desirable.

Another modification related to the recommended approach to CAP severity assessment. In TG14 two severity assessment tools are recommended, SMART-COP and CORB, with no preference given to either. A decision was made to specifically recommend CORB in the local guideline for a number of reasons. Firstly, CORB only requires consideration of four easy to remember variables. In addition, only vital signs needed by CORB, in contrast to SMART-COP, where two laboratory tests, blood pH and serum albumin, are also required. Finally, the CORB severity score less complicated to calculate, with each variable scoring one point; whereas SMART-COP is complex to calculate (some variables score one and some others score two, and the score for some variables is age dependent). For those reasons, it was felt that CORB was a more pragmatic tool, particularly in busy clinical areas, such as ED, where most patients with CAP are initially assessed.

The CORB severity tool stratifies patients with CAP into one of the three severity groups; mild (score 0), moderate (score 1), and severe (score equal to or greater than 2). .

In order to promote adoption of the local CAP guideline recommendations, two different types of interventions were conducted during two consecutive periods of times (Figure 6.1).

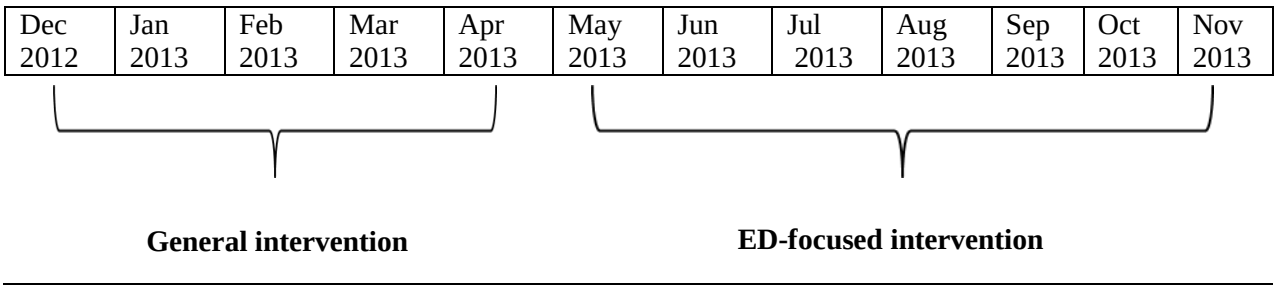


Figure 6.1: Intervention period timeline.

6.2.2. General intervention

An email was sent to all RHH medical staff advising them of the release of the local CAP guideline. The release of the guideline was combined with educational sessions. Four presentations and six group discussions were held during December 2012, and two presentations and five group discussions were conducted during February 2013. The content of these was developed and reviewed by the RHH AMS team to provide background to the development of the CAP guideline and the content. The key messages included:

- The involvement of key opinion leaders from all related departments in the development of the guidelines
- The recommended CAP severity assessment tool
- Ceftriaxone only being recommended as a first-line therapy for patients with severe CAP
- The adverse effects related to the use of ceftriaxone

All educational sessions were led by the research team with full support from the RHH AMS team.

Wall posters, with guideline recommendations and key messages, were displayed in all RHH medical departments (Figure 6.2). Furthermore, a lanyard card summarising the severity assessment tool and CAP guideline recommendations was distributed during the educational meetings (Figure 6.3). The pharmacy department subsequently assisted in further dissemination of lanyard cards to other medical staff who had not attended educational sessions.

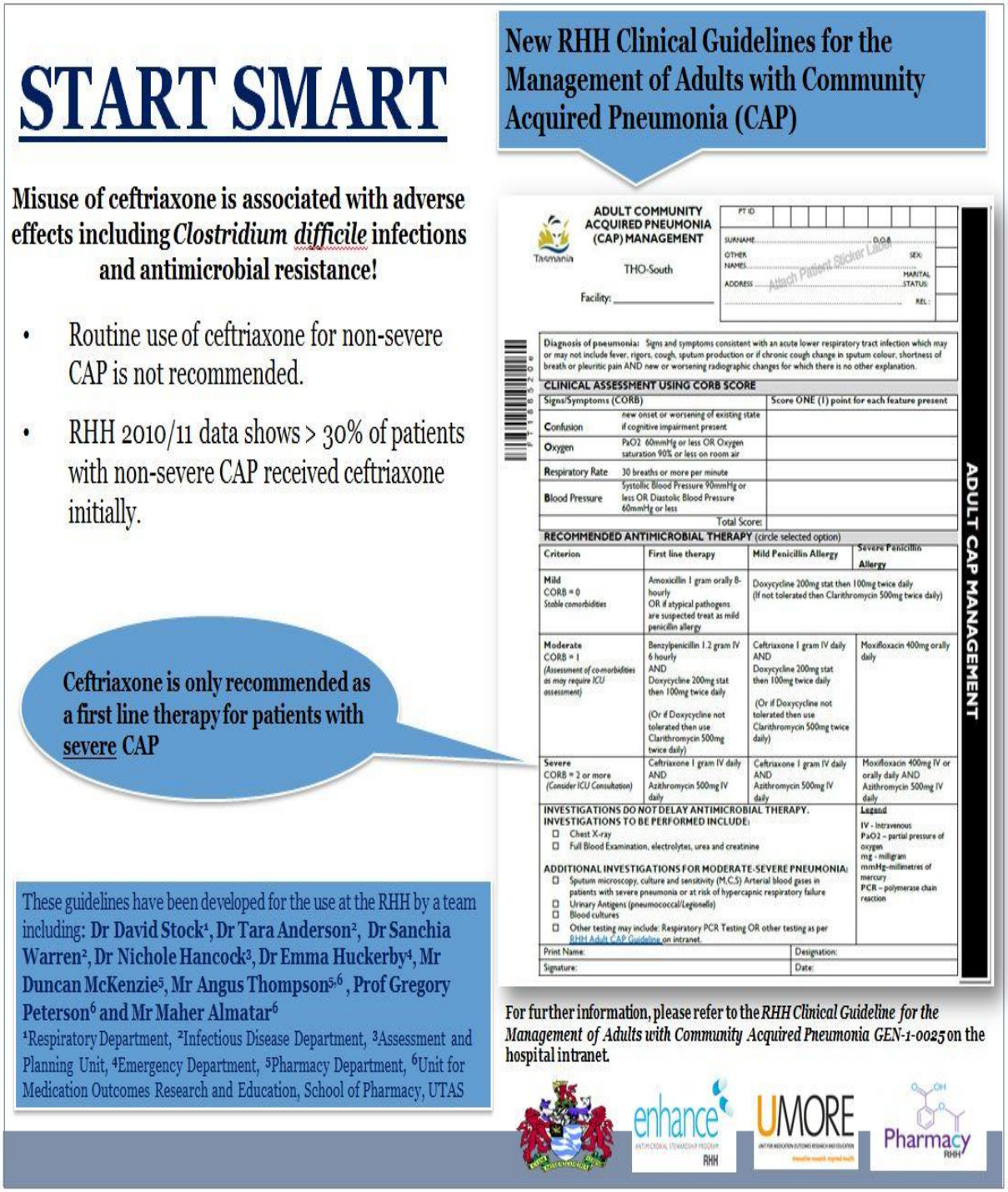
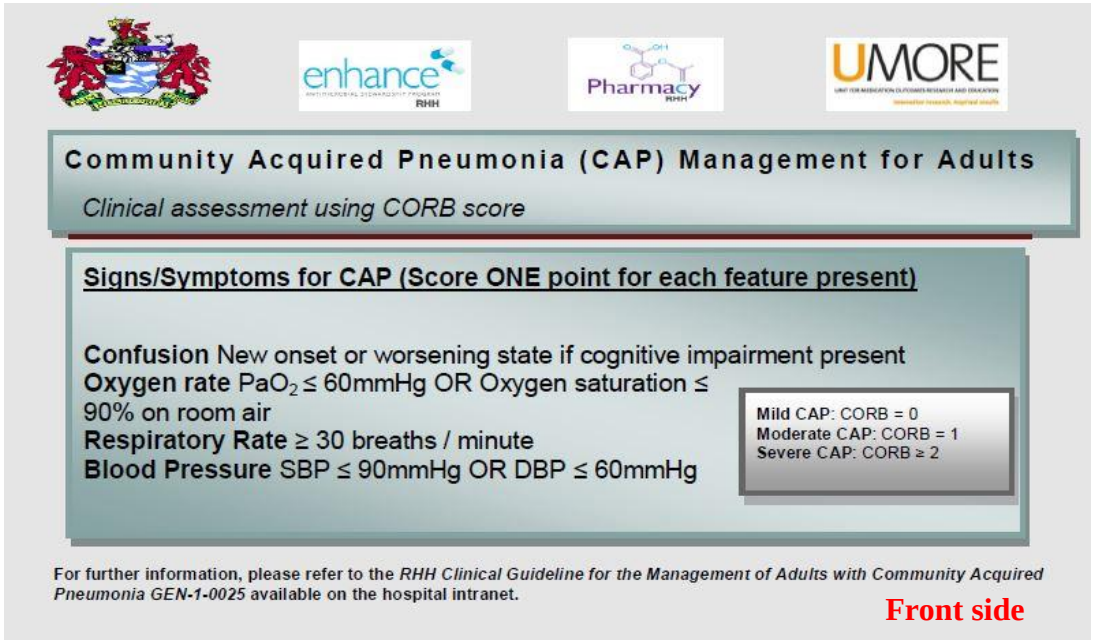


Figure 6.2: Poster component of intervention, as placed in the RHH medical departments.



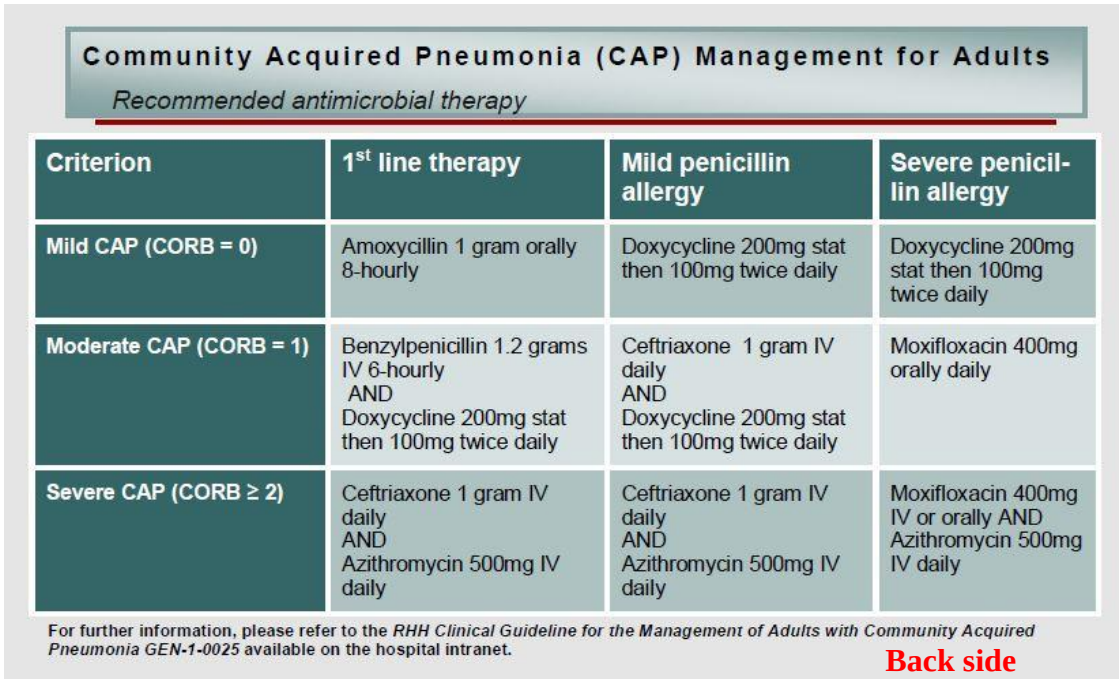


Figure 6.3: Lanyard card component of intervention, as distributed to RHH medical staff.

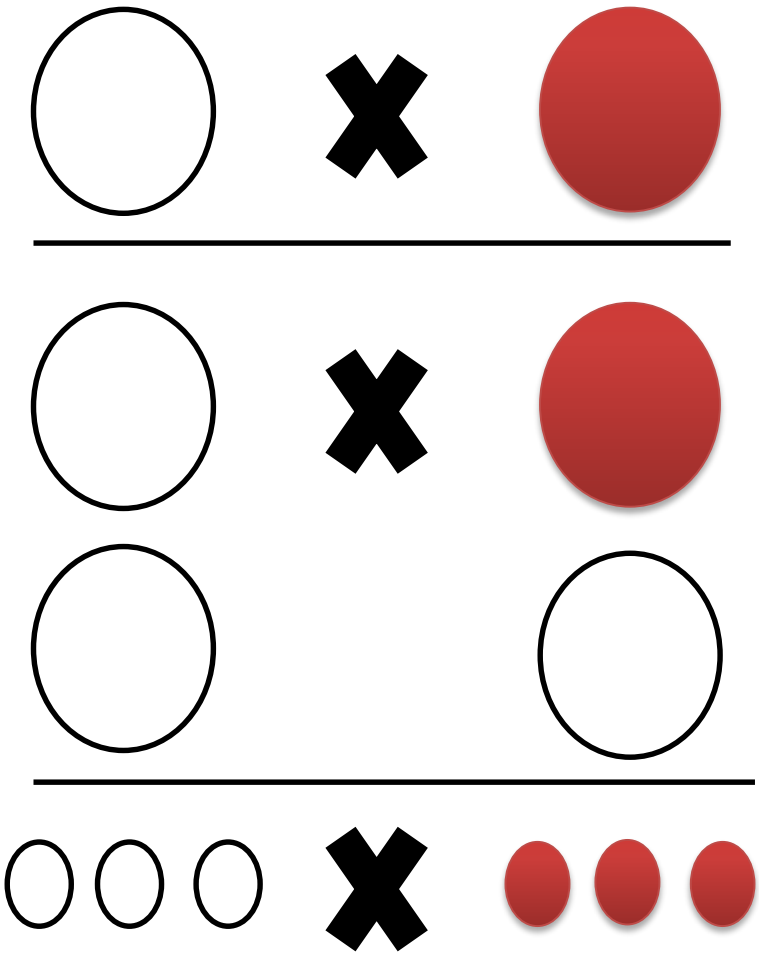
6.2.3. ED-focused intervention

During the next phase of the study, interventions were focussed on the ED (May 2013 to November 2013). A one-page CAP clinical pathway based on the local guidelines was developed and made available in the ED (Appendix I). The CAP clinical pathway was designed to complement the CAP guideline and provide ED staff with clear information to support appropriate management of CAP. The pathway contained information on the CORB severity assessment tool and the recommended antibiotic regimens based on the severity score. Two educational sessions were performed with ED nursing staff in order to raise awareness and promote utilisation of the clinical pathway by medical staff who treat patients with suspected CAP. Furthermore, an email was sent to all medical and nursing staff in the ED to advise them of the presence of the CAP clinical pathway and its location in the ED.

This was followed by monthly feedback on the management of 10 randomly selected patients with CAP. The feedback was sent from the stewardship team to the head of the ED department for onward distribution to ED medical staff (Appendix J).

6.3. Approaches to evaluate the impact of the multifaceted intervention

The evaluation of intervention studies in clinical settings in real time is challenging. This is because changes in practice often taken place gradually over time and randomising cohorts of patients to standard practice vs. best practice has major ethical limitations (339). This is why quasi-experimental designs, such as controlled and uncontrolled before-after and interrupted time series analysis are more suited to interventions that are carried out in clinical settings (Figure **6.4**) (339, 340) .



Uncontrolled Before-after approach

Controlled Before-after approach

Interrupted Time series approach

Figure 6.4: Study design approaches to assess the effect of an intervention on the quality of care.

The following sections briefly describe the advantages and disadvantages of the various experimental approaches that could be applied to assess the impact of the intervention and provides a justification for the methods chosen.

Uncontrolled before–after approach

In this study design, data is collected in two time periods, before and after the introduction of an intervention, in order to try and demonstrate a significant change. However, this study design is relatively weak in terms of evaluating quality improvement interventions (339). It has been shown that the uncontrolled before and after approach overestimates the results of interventions when compared to a controlled approach (341). For example, other confounding factors might lead to changes in the measured outcomes which might be not related to the intervention itself. Therefore, it has been suggested that this approach should not be used to evaluate an intervention, and if it is used, the data must be interpreted with caution (339).

Controlled before-after approach

In this approach, a researcher attempts to evaluate the effect of an intervention in the presence of a control group, where the intervention is not applied. The data is collected before and after the introduction of a quality improvement intervention in both study groups (339). The outcome measurement during the post-intervention phase is then evaluated and a significant difference between the two groups would be assumed to be due to the intervention. Using this approach would overcome the problem of the sudden and secular changes that are found when using the uncontrolled before-after approach (150). However, it would be sometimes difficult to find a control group during the baseline period that has similar outcome measurement to the intervention group.

Interrupted-Time series approach

This approach is designed to evaluate the effect of interventions at multiple equal time periods before and after interventions (342). When collecting data from a single study site to measure the effect of quality improvement interventions, interrupted-time series approach is always preferred over the simple uncontrolled before-after approach (150). A number of advantages might lead to a preference for using this approach over the before-after approach. Firstly, this is an alternative method to overcome the issues from the uncontrolled before-after design, and when it is difficult to find a comparable control group for the controlled before-after approach (339). Secondly, more information would be obtained by using this approach by allowing researchers to evaluate direct and latent effects of the intervention visually and statistically (343). This could not be evaluated by using the before-after approach. However, the impact of other factors that would occur at the same time as the intervention could not be assessed by this approach. Finally, a significant change that might be found when using the uncontrolled before-after approach might not be due to the intervention itself, and it might be due to an already increasing trend during the pre-intervention period (Figure 6.5). For example, a UK study was conducted to assess the effect of mailing guidelines on the use of radiographic examination to 376 general practitioners. The simple before-after approach indicated that the intervention had a significant impact, and fewer referral requests were observed after the introduction of the intervention. However, the interrupted time-series analysis showed a non-significant difference (344).

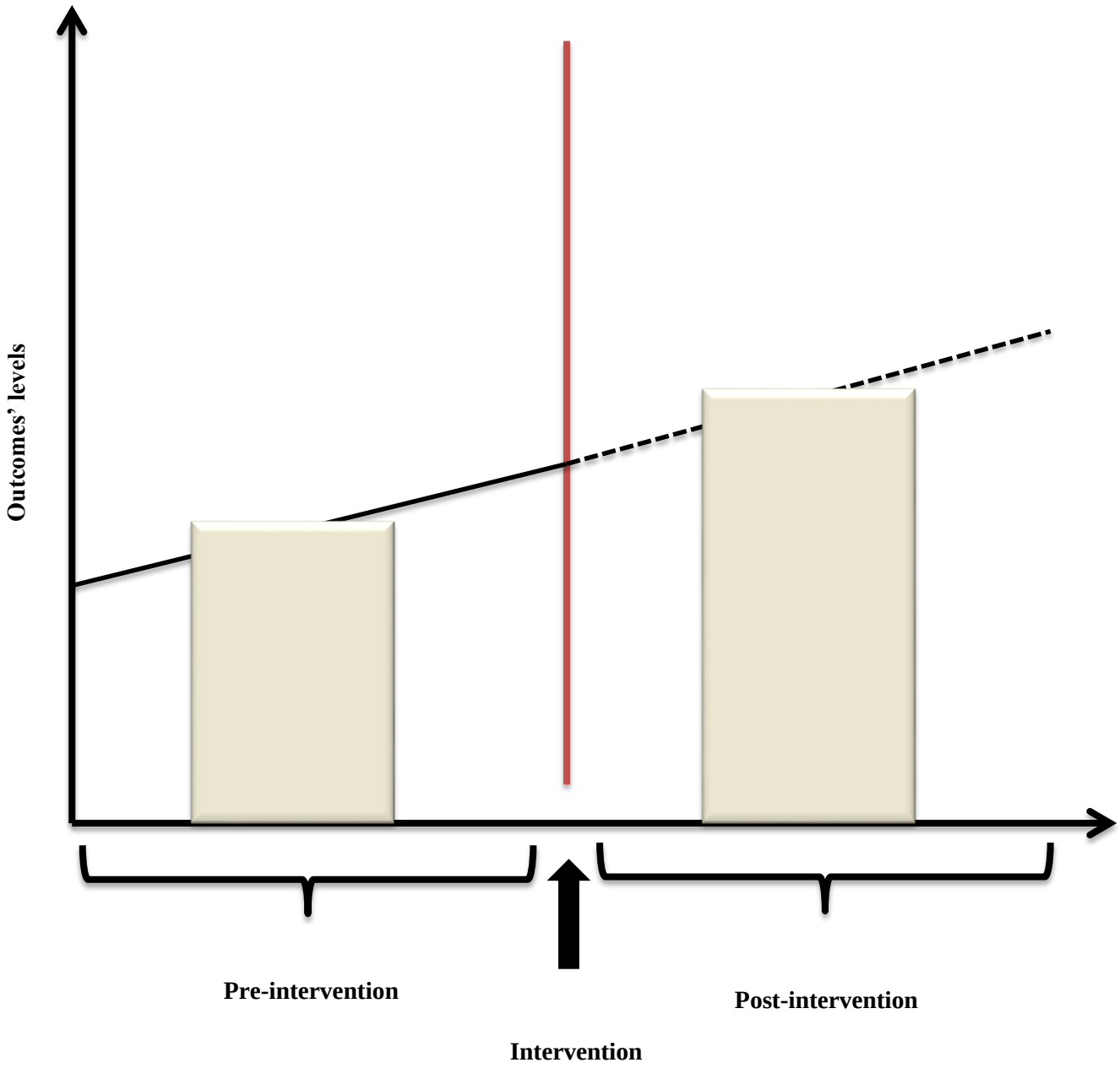


Figure 6.5: Uncontrolled before-after vs interrupted time series approaches.

For a better understanding of the effect of our intervention on prescribing behaviour, two approaches were utilised to analyse the data:

1- **Controlled before-after approach:** for this approach, the North West Regional Hospital (NWRH) was assigned as a control site and the RHH was assigned the intervention site. The RHH was selected as the site for intervention for several reasons. Firstly, the RHH has a well-established AMS program which would facilitate applying intervention strategies, whereas at the NWRH there was no AMS program at the time the study started. Secondly, the study to identify potential barriers to guideline adherence was conducted at the RHH and as discussed earlier, the whole project utilised an intervention designed to overcome the identified barriers. Finally, the RHH was conveniently located in close proximity to the investigators base.

2- **Interrupted time-series approach:** this approach was selected because two different intervention strategies were applied for two consecutive periods of time at the study site. Furthermore, the interventions were continuously applied during the whole intervention period. Therefore, the interrupted time-series approach would be useful to evaluate the effect of the different strategies over time, which could not be provided by using the previous approach. However, with the simple interrupted time-series analysis design, the main drawback is that other events might occur at the same time as the intervention and produce the same effect as the intervention. Therefore, using a combination of this method and the controlled before-after approach was deemed the most appropriate way to overcome this threat to internal validity.

6.4. Conclusions

This chapter has briefly described the background and rationale for the chosen multifaceted intervention strategies to improve CAP management at the RHH. Evaluation approaches to assess real time interventions were also discussed followed by the rationale for the adopted approaches. The next two chapters will present the results of this multifaceted intervention at the study hospital.

Chapter 7. Evaluating the impact of a tailored multifaceted intervention to improve the management of community-acquired pneumonia: A controlled before and after study design

7.1. Introduction

Debate continues about the best strategies to improve adherence to clinical practice guidelines (155). In recent years, there has been increasing interest in investigating those interventions designed to overcome barriers to the adoption of recommendations in CAP guidelines (153, 154). Studies show that interventions to improve adherence to clinical practice guidelines are more likely to improve a process of care when they take into account the existing barriers to adherence (154, 345-348). Thus, identification of these barriers would help an authoritative hospital group, such as AMS team, to determine the best strategies to promote adoption of clinical practice guidelines.

Our baseline study (Chapter 2) indicated poor adherence to TG14 for the empirical CAP management at both the RHH (intervention site), and the NWRH (control site). A major finding was that, the broad-spectrum third-generation cephalosporin, ceftriaxone, was frequently prescribed for patients with non-severe CAP. Accordingly, two studies (one quantitative and one qualitative), were conducted at the RHH to gain a better understanding of why physicians frequently failed to adhere to the TG14 recommendations for CAP management (Chapter 3 and 4). Since most patients with CAP in the baseline study were initially assessed and received their first dose of antibiotics in the ED, we conducted a survey of Australian infectious disease pharmacists to characterise the strategies they have used to improve antibiotic prescribing for CAP in the ED (Chapter 5). Based on our collective understanding from earlier studies (Chapter 3, 4 and 5), we designed an intervention to enhance the uptake of the recommendations in CAP guidelines (Chapter 6).

Traditionally, studies investigating the impacts of interventions on CAP management have used an uncontrolled before and after study design at a single institution (181, 250, 349). However, there are certain drawbacks associated with use of this approach. This approach might overestimate the results of interventions (341). For example, this approach fails to control for secular trends and sudden changes to the quality improvement intervention (339). Until recently, there has been no published Australian research investigating the effect of an intervention to improve CAP guideline adherence with the presence of a control group. Therefore, by including the NWRH where no intervention was made, we were able to control for some variables that may have affected the reliability of our findings.

The aims of this chapter were:

1- To evaluate the impact of the intervention on adherence to the CAP guidelines
2- To evaluate the impact of the intervention on ceftriaxone prescribing
3- To assess the impact of the intervention on clinical outcomes, specifically patient mortality and length of stay (LOS)

7.2. Methods

7.2.1. Study design and setting

A retrospective, controlled, before-after, study was performed. Baseline data was collected in the period between July 2010 and March 2011 and the subsequent data collection period from December 2012 to November 2013 covered the periods during and after the release of the local CAP guidelines and implementation of interventions.

7.2.2. Inclusion and exclusion criteria

All patients (age ≥ 18 years) admitted with a suspected diagnosis of CAP within 24 hours of the presentation at the ED in both hospitals during the study period were screened for eligibility. Patients were considered as having CAP if this diagnosis was documented in their medical notes or either the physician or radiologist indicated a change consistent with pneumonia on the chest X-ray. Patients with pneumonia were excluded if they were admitted from a nursing home (NH), previously admitted to a hospital within 14 days of the current presentation, immunosuppressed (chronic use of prednisolone, had received chemotherapy within 3 months, were taking any other immunosuppressive agents for the management of solid organ transplantation or were HIV positive), had co-existing cystic fibrosis or bronchiectasis, or where the patient files were incomplete. These are the same patient selection criteria applied to the baseline study.

7.2.3. Data collection

All patients' files were reviewed retrospectively by a trained clinical research pharmacist in both hospitals and information was collected using a structured data collection form. The abstracted information included patients' demographics, clinical history, and first prescribed antibiotic regimens. Severity of CAP was assessed using relevant clinical and laboratory parameters as described earlier in Chapter 2 and shown in Appendix A.

7.2.4. CAP guideline adherence and patients' clinical outcome measurements

Adherence to the CAP guidelines was assessed against the TG14 recommendations. Although physicians at the RHH were expected to follow the hospital's local CAP guidelines, these were developed from and were largely consistent with the recommendations in TG14 as discussed in an earlier chapter (Chapter 6). Patients were considered to have received a guideline concordant regimen if they met the following criteria: 1) concordant selection of antibiotic/s, and 2) concordant route of administration. Clinical outcome assessment included hospital LOS and rates of in-patient mortality.

7.2.5. Definitions

Throughout this chapter, the term "intervention site" will be used to refer to the RHH, while the term "control site" refers to the NWRH. In addition, the term "intervention group" will refer to data from the RHH during the intervention period, while the term "non-intervention group" will refer to all baseline data plus the data from the NWRH during the intervention period

7.2.6. Statistical analysis

Descriptive statistics included frequencies, percentages, means, medians and standard deviations. Normality of the data distribution was examined using normality curve and Shapiro-Wilk tests. To compare categorical and continuous variables with non-normal distribution between the intervention and control groups Chi square, Wilcoxon rank sum and Fisher's exact tests were used as per the analysis needs. To compare between normally distributed continues variables, Student's t and nonparametric Wilcoxon rank sum tests were employed.

Logistic regression was performed with adherence to the guideline as the dependent variable. Patient demographics, Charlson's comorbidity index, presence of chest x-ray change, severity and the four cohort groups (control and intervention sites, before and after the introduction of the intervention) were analysed against adherence to the guidelines. A cut-off p value of <0.25 was used to include variables in the regression analysis as recommended by experts in the field (350). It has been shown that using the conventional *P* value cut-off point of < 0.05 could fail in identifying some variables known as influential (351).

To assess the impact of the intervention on clinical outcomes, the data from the intervention site during the intervention period were compared to the collective data of the groups who had not been exposed to the intervention (control site and the intervention site before the introduction of the intervention). Patients' characteristics were compared between the two groups to identify any other variables that may have influenced the results.

All statistical analyses were performed using IBM SPSS statistics for windows, version 20.0. Armonk, NY: IBM Corp. *P* values less than 0.05 were considered significant.

7.2.7. Ethical approval

Prior to commencing the study, ethical approval was sought from and granted by the Tasmanian Health and Medical Human Research Ethics committee (Approval numbers: H0011729; H0012810).

7.3. Results

The pre-intervention group who were admitted to the RHH (intervention site) with a suspected diagnosis of CAP consisted of 276 patients. Of these, 83 (30.1%) patients were excluded. The intervention period ran from 1 December 2012 through to 30 November 2013. During this period, 425 patients at the intervention site were screened for inclusion, of whom 157 (36.9%) were excluded. For the NWRH (control site), 68 patients were assessed for eligibility during the baseline period and 15 (22.1%) of these were excluded. During the intervention period, the control site consisted of 183 patients, where 73 (39.9%) patients were excluded. The reasons for these exclusions are summarised in Table 7.1.

Table 7.1: Reasons for exclusion from the study.

Exclusion criteria	**Intervention site**		**Control site**	
	Baseline	Intervention period	Baseline	Intervention period
Hospital admission in the previous 14 days	21	44	5	26
Immunosuppressed patients	38	70	7	28
NH	22	31	1	14
No antibiotic prescribed within 24 hours of admission	1	3	2	3
Bronchiectasis	1	6	-	2
Fibrosis	-	1	-	-
Incomplete file	-	2	-	-
Total	83	157	15	73

7.3.1. Patients' characteristics

Patient characteristics from the intervention and control groups before and after the intervention are shown in Table 2. As evident from Table 7.2, most characteristics were similar between intervention and control groups apart from some differences in the severity of CAP and comorbidity index score. Comparing the intervention and baseline populations, there were significantly more patients with a severe pneumonia at the intervention site (32.8% vs. 24.4% $p < 0.05$) and significantly less patients with mild pneumonia at the control site (33.6% vs. 58.5%; $p < 0.05$).

A difference in the severity profile was also seen between both sites during the baseline period. Moreover, amongst patients in the control site, the comorbidity index score were greater during the intervention period (4.7 vs. 3.6; $p < 0.01$), and changes in the chest X-ray were more likely to be seen (71.8% vs. 50.9%; $p < 0.05$). A higher comorbidity index score was seen in patients at the intervention site during the baseline phase. However, there were no significance differences in patients' characteristics, apart from the mild CAP, between the non-intervention group and the intervention group (Table 7.3).

Table 7.2: Patients' characteristics in the intervention and control sites before and during the intervention.

Patients' characteristics	Intervention site (RHH)		Control site (NWRH)	
	Baseline (N = 193)	Intervention period (N = 268)	Baseline (N = 53)	Intervention period (N = 110)
Gender (male)	105 (54.4)	154 (57.5)	30 (56.6)	66 (60)
Age (years)	69.2 ± 16.1; 71	66.8 ± 18; 70	64 ± 18; 70	68.6 ± 16.6; 73
Prior antibiotic/s within 7 days	43 (22.3)	45 (16.8)	8 (15.1%)	25 (22.7)
Charlson's comorbidity index	4.8 ± 2.3; 5 [a]	4.3 ± 2.5; 4	3.6 ± 2.1; 4 [a]	4.7 ± 2.5; 5
Penicillin allergy	30 (15.5)	37 (13.8)	8 (15.1)	17 (15.5)
Change in chest X-ray	117 (60.6)	175 (65.3)	27 (50.9)	79 (71.8)
Severity				
Mild CAP	64 (33.2)[a]	78 (29.1)	31 (58.5) [a]	37 (33.6)
Moderate CAP	82 (42.5)[a]	102 (38.1)	9 (17) [a]	40 (36.4)
Severe CAP	47 (24.4)	88 (32.8)	13 (24.5)	33 (30)

Data are presented as number (%) for categorical variables and mean ± standard deviation; median for numerical variables

Coloured cells indicate a significant difference ($p < 0.05$) at the same site before and after intervention.

[a] P value < 0.05 between the intervention and control sites within the same period of time.

Table 7.3: Patients' characteristics in the intervention group and non-intervention groups.

Patients' characteristics	Intervention group (N = 268)	Non-intervention groups (N = 356)
Gender (male)	154 (54.1)	201 (56.5)
Age (years)	66.8 ± 18; 70	66 ± 16.3; 71
Prior antibiotics/s within 7 days	45 (16.8)	76 (21.3)
Charlson's comorbidity index	4.4 ± 2.5; 4	4 ± 2.3; 5
Penicillin allergy	37 (13.8)	55 (15.4)
Change in chest X-ray	175 (65.3)	223 (62.6)
Severity		
Mild CAP [a]	78 (29.1)	132 (37.1)
Moderate CAP	102 (38.1)	131 (36.8)
Severe CAP	88 (32.8)	93 (26.1)

Data are presented as number (%) for categorical variables and mean ± standard deviation; median for numerical variables

[a] *P* value < 0.05

7.3.2. Adherence to guidelines for empirical CAP management

Adherence rates to the TG14 recommendations regarding management of CAP during the baseline and intervention periods are illustrated in Table 7.4. As can be seen, the adherence rate to recommendations at the control site during the intervention period was 11.6% higher than that seen in the baseline period; however, the deference was not statistically significant. . However, the rates of adherence significantly increased at the intervention site during and after the intervention period, and this improvement occurred across all CAP severity grades.

Table 7.4: Adherence to the TG14 for the empirical management of CAP within and between groups.

Adherence to TG14, by patient group	**Intervention site**		**Control site**	
	Baseline	Intervention period	Baseline	intervention period
Mild CAP				
Total no.	64	78	31	37
Appropriate regimen	2 (3.1)	21 (26.9) [a]	1 (3.2)	2 (5.4) [a]
Moderate CAP				
Total no.	82	102	9	40
Appropriate regimen	17 (20.7)	58 (56.9) [a]	1 (11.1)	6 (15) [a]
Severe CAP				
Overall				
Total no.	47	88	13	33
Appropriate regimen	12 (25.5)	55 (62.5) [a]	2 (15.4)	13 (39.4) [a]
Overall				
Total no.	193	268	53	110
Appropriate regimen	31 (16.1)	134 (50) [a]	4 (7.5)	21 (19.1) [a]

Data are presented as number (%).
Coloured cells indicate a significant difference ($p < 0.05$) at the same site before and after intervention.
[a] P value < 0.05 between the intervention and control sites within the same period of time.

Logistic regression analysis was employed. Patient demographics, comorbid conditions, presence of chest X-ray change, severity and being in the intervention group were analysed against adherence to the guidelines, as shown in Table 7.5.

Table 7.5: Patients' characteristics depending on the guideline adherence.

Variables		Received concordant regimen (N = 190)	Received discordant regimen (N = 434)
Intervention group [a]		134 (70)	134 (30.9)
Gender (male)		104 (54.7)	251 (57.8)
Age; mean ± SD		68.3 ± 17.4	67.3 ± 17.2
Penicillin allergy		27 (14.2)	65 (15)
Comorbidity index; mean ± SD		4.4 ± 2.3; 4	4.6 ± 2.5; 4
Change in chest X-ray		63 (33.2)	163 (37.6)
Severity [a]	**Mild**	26 (13.7)	184 (42.4)
	Moderate	82 (43.2)	151 (34.8)
	Severe	82 (43.2)	99 (22.8)
Prior antibiotics/s within 7 days		32 (16.8)	89 (20.5)

Data are presented as Number (%).

[a] *P* value < 0.25

Of all the independent factors included in the univariate analysis, only two variables showed a significant effect in influencing TG14 adherence (intervention and severity). A binary logistic regression was performed to identify the effects of these variables on the likelihood of receiving a concordant regimen according to TG14 recommendations for the management of CAP. The logistic regression model was significant ($P < 0.05$). This model explained 27.1% of the variance based on Nagelkerke R square. The model correctly classified 73.1% of the cases. The model had 28.9% sensitivity, where the model predicted 28.9% of the guideline adherence. The specificity was 92.4%, where the model predicted 92.4% of the non-adherence to the guideline. Of all cases that were predicted to receive a concordance regimen 62.5% were correctly predicted (positive predictive value). On the other hand, of all cases that were predicted as not having a concordant regimen, 74.8% were predicted correctly (negative

predictive value). The odd of being treated with a guideline-concordant regimen in the intervention group was 5.5 times that of the control group when severity was held (Table 7.6).

Table 7.6: Logistic regression analysis of variables associated with adherence to CAP recommendations as per TG14.

Factor	OR	95% CI	*P*
Intervention	5.5	3.7 – 8.1	< 0.05
Severity	2.3	1.8 - 3	< 0.05

7.3.3. Ceftriaxone usage

Changes in ceftriaxone prescribing were compared between intervention and non-intervention groups. As shown in Figure 7.1, there was an overall 7% reduction in ceftriaxone prescribing in the intervention group compared to the non-intervention group; nevertheless, the Chi-square test did not show this difference to be significant. Importantly however, the data shows that ceftriaxone prescribing for patients with non-severe CAP in the intervention group was significantly 16.2% less than that seen in the non-intervention group ($p < 0.05$). On the other hand, for those patients with severe CAP, no significant difference was seen in prescribing ceftriaxone between the two groups.

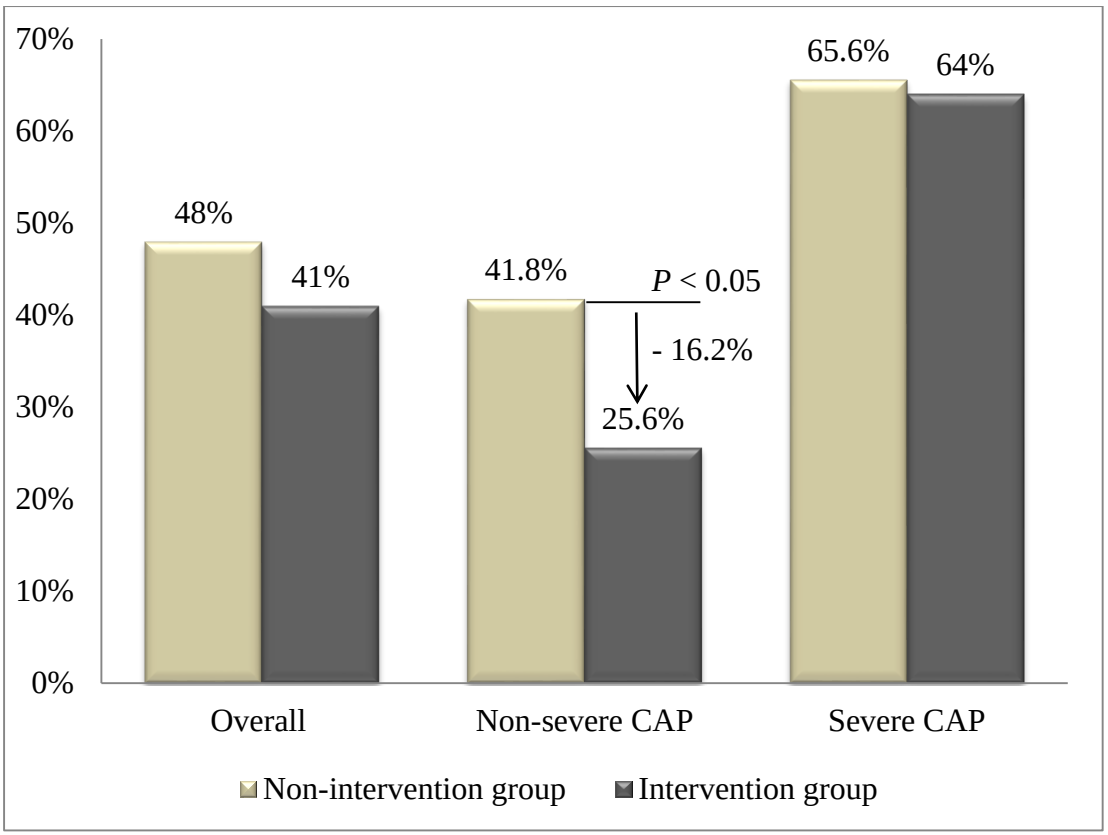


Figure 7.1: Ceftriaxone-based therapy prescribing rates in the intervention and non-intervention groups.

7.3.4. Patients' clinical outcome measurements

Table 7.7 compares patients' length of stay (LOS) and mortality rates between the intervention and non-intervention groups. As the table shows, LOS was not different between the two groups. Nevertheless, sub-group analysis revealed patients with non-severe CAP in the intervention group have an average LOS 0.8 days shorter than the control group ($p < 0.05$). The in-patient mortality was 3.9% significantly lower ($p < 0.05$) in the intervention group when compared to the non-intervention groups (Table 7.7). As shown in table 7.7, the sub-group analysis revealed that in-patient mortality was lower in the intervention group compared to the non-intervention group, for both severe (8% vs. 18.3%, $p < 0.05$) and non-severe CAP cases (1.1% vs. 3.4%, $p < 0.05$).

Table 7.7: Patients' clinical outcomes.

Clinical outcome	Non-intervention group	Intervention group
All Patients		
Patients' number	356	268
LOS (days)	5.8 ± 5.4; 4	5.9 ± 7.5; 4
In-patient mortality [a]	26 (7.3)	9 (3.4)
Patients with severe CAP		
Patients' number	93	88
LOS (days)	7.1 ± 6.2; 5	8.8 ± 8.5; 6.5
In-patient mortality [a]	17 (18.3)	7 (8)
Patients with non-severe CAP		
Patients' number	263	180
LOS (days) [a]	5.3 ± 5; 4	4.5 ± 6.7; 3
In-patient mortality	9 (3.4)	2 (1.1)

Data are presented as number (%) for categorical variables and mean ± standard deviation; median for numerical variables
Deaths are excluded from the analysis of LOS outcomes
[a] *P* value < 0.05

Regarding the impact of adherence to CAP guideline recommendations on clinical outcomes, our data indicated a trend of decreased overall mortality rate among patients who received a concordant regimen (4.2% vs 6.2%; $p = 0.32$). Moreover, the mortality rates were even lower among patients with severe CAP who received concordant antibiotic regimens (8.5% vs 17.2%; $p = 0.09$). However, none of these differences were statistically significant (Table 7.8).

Table 7.8: Patients' clinical outcomes and concordance with antibiotic regimens.

Clinical outcome	Received concordant regimen	Received discordant regimen
All Patients		
Patients' number	190	434
LOS days	6.4 ± 7.6; 4	5.6 ± 5.8; 4
In-patient mortality	8 (4.2)	27 (6.2)
Patients with severe CAP		
Patients' number	82	99
LOS days	7.9 ± 6.7; 5	7.9 ± 8; 6
In-patient mortality	7 (8.5)	17 (17.2)
Patients with non-severe CAP		
Patients' number	108	335
LOS days	5.3 ± 8; 3	4.9 ± 4.8; 4
In-patient mortality	1 (0.9)	10 (3)

Data are presented as number (%) for categorical variables and mean ± standard deviation; median for numerical variables
Deaths are excluded from the analysis of LOS outcomes

7.4. Discussion

The objective of this study was to evaluate the effectiveness of an intervention designed to overcome potential barriers to guideline adherence. This study showed that active implementation of CAP guidelines had a desirable impact on prescribing practice for empirical CAP management, with concomitant improved clinical outcomes. The current study found that adherence to the CAP guideline recommendation significantly improved during the intervention period from 16.1% to 50%. Furthermore, ceftriaxone prescribing was reduced by 16.1% for patients with non-severe CAP in the intervention group. The study also found that the improved adherence to guidelines has been associated with reducing mortality rates and decrease in LOS.

Intervention strategies thought to improve adherence to CAP management guidelines have been demonstrated in several studies (352). However, there is no agreement surrounding what is the best strategy (155). Therefore, it has been strongly suggested that a multifaceted intervention strategy be used to promote adherence to guidelines (117, 129). It has also been found that interventions could have a more positive impact when designed to overcome those factors that have been identified previously as barriers to the desired prescribing habits (154).

This study strongly suggests that a tailored multifaceted intervention significantly improves adherence to guidelines for empirical management of CAP. These findings are consistent with the findings of Jeroen *et al.*, which showed that tailoring multifaceted interventions to address identified barriers in a hospital setting could lead to a significant improvement in guideline adherence for the management of lower respiratory tract infections when compared to interventions which did not consider potential barriers (154). However, our study differs from this work, in that we made no intervention at all in the control site.

Besides the influence of the interventions on adherence to CAP recommendations, the logistic regressions analysis indicated that adherence was more likely to be influenced by the severity of the diseases. These results must be interpreted with caution because ceftriaxone-based therapy prescribing was common in the non-intervention group. Therefore, high adherence to the therapeutic guidelines for patients with severe CAP might be due to co-incident use of ceftriaxone-based therapy.

This finding corroborates the thinking of van der Velden *et al.* who suggested that non-adherence to the recommended guidelines is significantly associated with more broad-spectrum antibiotic prescription (314) .

Our findings not only indicated an increase in adherence to CAP guidelines, but also demonstrated a significant decrease in prescribing of ceftriaxone for patients with non-severe CAP. According to national and international guidelines regarding the empirical management of CAP, patients are divided into groups either by severity or the site of care, and recommendations regarding antibiotic regimens are made accordingly (144, 182, 186). With this strategy, the broadest-spectrum antibiotic regimens are reserved for patients with severe CAP or those who are admitted to intensive care units. Therefore, our findings were consistent with one of the main aims of antimicrobial stewardship. This is to reduce unnecessary use of broad-spectrum antibiotics in order to reduce antibiotic resistance pressures and serious adverse effects, such as CDI (31). As a response to these issues, many initiatives have been conducted to reduce the consumption of these broad-spectrum antibiotics in order to decrease the emergence of difficult-to-treat microorganisms (86, 353, 354). For example, in a study conducted by Talbaert *et el.*, the authors found that their antimicrobial stewardship activities have been associated with a reduction in the consumption of broad-spectrum antibiotics such as cephalosporins and fluoroquinolones, which was consequently associated with a significant decrease in the incidence of CDI (86).

Another notable finding from our study was the improved clinical outcomes (mortality and LOS) for patients in the intervention group. These key results seem to be consistent with other studies, which found that active implementation of CAP guidelines was associated with improved clinical outcomes (259). What is surprising is that the significant improvement in clinical outcomes in the intervention group was observed despite this group including a higher proportion of patients with severe CAP compared to population in the baseline study. In our study, this was associated with a significant improvement in the adherence to the CAP recommendations regarding the empirical management of CAP. Previous studies have demonstrated that adherence to CAP guidelines is associated with a reduction in both LOS and mortality rates. For example, in their study looking at the impact of adherence to CAP guidelines on the clinical outcomes, Chen *et al.* were able to show that patients who received a concordant regimen were more likely to be discharged earlier than those who did not (355). In term of mortality, studies show that adherence to guidelines significantly improves the survival rate among patients with CAP (356, 357). For instance, Nathan *et al.* argued that adherence CAP guidelines would save 20 lives every year in the US hospital setting (263). Furthermore, a study conducted in 1725 hospitalised elderly patients (age $\geq$ 65 years) with a principal diagnosis of pneumonia, found that besides a reduction in LOS and time to clinical stability, the patient group that received concordant-guidelines regimens had a 9% lower mortality rate than those who received discordant regimens (244). In our study, the overall mortality rate was significantly lower in the intervention group when compared to the non-intervention group. Moreover, the gap in the survival rate increased by 10% for patients with severe CAP. This finding is consistent with a study that was conducted on CAP patients were admitted to the ICU (284). This study found that the in-hospital mortality rate was 9% less for the group of patients who received antibiotic regimens based on guideline recommendations. However, it is important to bear in mind that despite the improvement in clinical outcomes

among patients in our intervention group, we could not find a direct association between improved clinical outcomes and adherence to guidelines

The published association between the mortality rates and the prescription of the recommended antibiotic regimens has influenced recommendations for the management of CAP. For example, the British Thoracic Society and Infectious Diseases Society of America/the Society for Healthcare Epidemiology of America guidelines for the management of CAP advocate the use of CURB65 severity scoring system, which is based on predicting mortality from CAP, to stratify patients into severity groups (182, 186).

One of the issues that emerged from these findings is that, despite the significant improvement in the clinical outcomes in the intervention group, a further analysis failed to find a significant direct association between the adherence to the guideline and the change in clinical outcomes when compared with the group who did not receive the intervention. The failure to reject the null hypothesis might be explained by the small sample size in both our groups. As an example, our data showed that in-hospital mortality rate was 8.5% (n = 7/82) in patients with severe CAP who received concordant antibiotic regimen, compared with 17.2% (n = 17/99) in patients who received a discordant regimen. Although the difference is almost 9% between the two groups, the Chi square test has failed to reach the level of statistical significance. To show such a difference between the two groups, approximately 254 patients would have been needed per group (at a power of 80% and $p = 0.05$).

7.5. Limitations

Several limitations to this study need to be acknowledged. First, the CAP guideline introduced as part of the intervention has minor deviations from TG14 and doctors in the intervention group were expected to follow the local guidelines, and the non-intervention groups were expected to comply with the TG14 recommendations. Nonetheless, adherence to guideline recommendations for all groups in our study was assessed against TG14. This was because the local guideline was based on TG14 and therefore considered to be a tool to promote adherence to the TG14 recommendations for CAP management. Secondly, the components of the intervention were sequentially delivered over a period of the time, and there was no data collected after the end of our intervention to assess the sustained impact of the implemented strategies. Therefore, the results must be interpreted with a degree of caution. Third, almost one-third of the patients were diagnosed with pneumonia with no detected changes in the chest X-ray, and their inclusion in the study was therefore based mainly based on the doctor's clinical judgment. However, although this might raise a question regarding the accuracy of the diagnosis, the main purpose of this study was to evaluate antibiotic prescribing practice when a doctor made a clinical decision to treat a patient as one with CAP. Fourth, different strategies were conducted in distinct consecutive times to improve adherence to the guideline recommendations. Nevertheless, this study could not identify the extent of the effect of individual strategies. Fifth, although we evaluated the impact of the intervention on two major clinical outcomes, mortality and LOS, other clinical outcomes, such as ICU admission, treatment failure, and time to clinical stability, which could be important, have not been investigated. Sixth, although there are a number of validated severity tools to assess the severity of CAP, we only used the CORB tool recommended by TG14 to determine severity and accordingly assess the prescribed antibiotic regimens. Finally, the study did not include patients with CAP who presented in the ED and were not admitted. Therefore, it is important

to bear in mind the possible bias in the study findings with regard to the antibiotic prescribing practice.

7.6. Conclusion

The current findings add to a growing body of literature on the impact of the antimicrobial stewardship interventions on changing prescribing practice among physicians and improving clinical outcomes. The results of the present study show that an intervention tailored to overcome identified barriers can successfully improve adherence to recommendations in CAP guidelines. The second major finding was an improvement in the clinical outcomes (LOS and mortality rates) among patients in the intervention group.

Chapter 8. Multifaceted intervention to improve adherence to management guidelines for CAP: Interrupted Time-series analysis

8.1. Introduction

One of the challenges in evaluating the impact of interventions in real time clinical settings is the absence of a control arm. As discussed earlier (Chapter 6), a number of types of study can be used to measure the effect of such interventions, including before and after, controlled before and after and interrupted time series designs (151, 274). Results from the previous chapter (Chapter 7), where the controlled before-after approach was utilised, indicated a positive impact of the intervention in the overall adherence to the CAP guidelines. However, the intervention included two phases, which were implemented in two consecutive time periods, one general and one focused on the ED (Chapter 6). Therefore, time series analysis was chosen as the most appropriate method to evaluate the impact of these distinct interventions strategies. The specific aim of this study was to:

- Determine the impact of different strategies over time at the RHH, in order to highlight the most effective approaches to improving adherence to CAP guidelines.

8.2. Methods

8.2.1. Study site, participants and data collection

This study was conducted at the RHH; with patient inclusion and exclusion criteria, data collection, and assessment of adherence methods exactly alike to those used in the study described in the previous chapter (Chapter 7).

8.2.2. Data analysis

Data were collected on a monthly basis for the period between July 2012 and November 2013, providing five data points for pre-intervention phase, five data points during the general intervention phase and seven data points during the ED-focused intervention phase. To perform interrupted time series analysis, the data was converted into percentages (monthly number of patients who received a guideline concordant CAP treatment regimen divided by the total monthly number of patients reviewed). These data were then plotted as a chart on a monthly basis to visualise the adherence rates over the study period.

The mean, standard deviation (SD) and standard error of the mean (SEM) for adherence rates at baseline, and during the general and ED-focused interventions were calculated. All samples were tested for significance between interventions using a one-way analysis of variance between groups (ANOVA) test. If statistical significance was detected, a post hoc analysis was carried out to examine any significant differences across individual time periods. All data are expressed as the mean ± standard error of mean (SEM). Significance was agreed at one-tail values of $p < 0.05$.

The statistical comparisons of patient characteristics and clinical outcomes were examined among the three time periods. The association between categorical data was examined using the Chi square test. Scaled date was examined using the Kruskal Wallis test. Statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY, USA).

8.2.3. Ethical approval

Ethical approval was granted by the Tasmania Health and Medical Human Research Ethics Committee [Approval number: H0012810].

8.3. Results

8.3.1. CAP cases

A total of 593 patients were assessed for eligibility, with 195 (32.9%) patients being excluded. The reasons of exclusions were recent hospital admission (n = 54), immunosuppressed patients (n = 86), aged-care facility residents (n = 39), no antibiotic prescribed within 24 hours of admission (n = 7), bronchiectasis (n = 6), cystic fibrosis (n = 1), and incomplete patient's file (n = 2). The remaining 398 patients were considered as eligible for the study.

Over the entire study period (July 2012 and November 2013), the average number of eligible patients per month was 23. This rate varied during the different phases of the study, with 26 per month pre-intervention (July to November 2012), 18 per month during the general intervention (December 2012 and April 2013) and 25 per month during ED-focused intervention (May to November 2013).

Patients' demographics and characteristics among the three phases are summarised in Table 8.1, from which it can be seen that there were no significant differences among the three groups.

Table 8.1: Patients' demographics and characteristics.

	Pre – intervention (N = 130)	General intervention (N = 90)	ED-focused intervention (N = 178)
Median age (years)	68	70.5	69.5
Gender (male)	81 (62.3)	54 (60)	100 (56.2)
LOS (days)	3 (1 - 20)	4 (1- 66)	3 (1 - 57)
Charlson comorbidity Index score	4 (0 – 12)	5 (0 – 11)	4 (0 - 12)
Change in chest X-ray noted	92 (70.7)	62 (68.9)	113 (63.5)
Severity			
Mild	40 (30.8)	29 (32.2)	49 (27.5)
Moderate	57 (43.8)	32 (35.6)	70 (39.3)
Severe	33 (25.4)	29 (32.2)	59 (33.1)
Documented penicillin allergy	20 (15.4)	13 (14.4)	24 (13.5)
Antibiotic therapy in the 7 days prior to admission	22 (16.9)	13 (14.4)	32 (18)
In-hospital mortality	7 (5.4)	4 (4.4)	5 (2.8)

Data are presented in numbers (%) for categorical and median (range) for scale variables

8.3.2. Exposure to the interventions

During the general intervention period, 39 medical staff working in the ED attended the educational sessions and of these, 21 were of a junior grade (interns and residents). The number of doctors who attended from the other medical departments was estimated at 50. The lanyard card, with the guideline recommendations for empirical CAP management, was given to all general medical (n = 120) and ED doctors (n = 40).

8.3.3. Time series analysis results

Figure **8.1** summarises the adherence rates to TG14 recommendations regarding empirical management of CAP for adults on a monthly basis, from July 2012 to November 2013; spanning the pre-intervention, general intervention and ED-focused intervention phases. It can be clearly seen that the adherence rates increased during the ED-focused intervention. Before the general intervention, the adherence rate began at 22.2% in July 2012. During the ED-focused intervention, adherence rates fluctuated between 40.9% and 77.3%. However, all data points in the ED-focused intervention phase were above those in the baseline and general intervention periods. The mean adherence percentages for the pre-intervention, general intervention and ED-focused intervention phases were 28.1 (SEM ± 1.82; SD ± 4.1), 31.2 (SEM ± 3.4; SD ± 6.8), and 61.5 (SEM ± 5.42; SD ± 14.3) respectively. One-way ANOVA test showed that there was a statistically significant difference among the three phases ($p < 0.001$). A post hoc analysis showed that the adherence rate significantly increased after the ED-focused intervention when compared to the pre-intervention ($P< 0.001$) and general intervention ($P<0.001$). Meanwhile, the adherence rate during the general intervention phase was not statistically different to that during the pre-intervention phase.

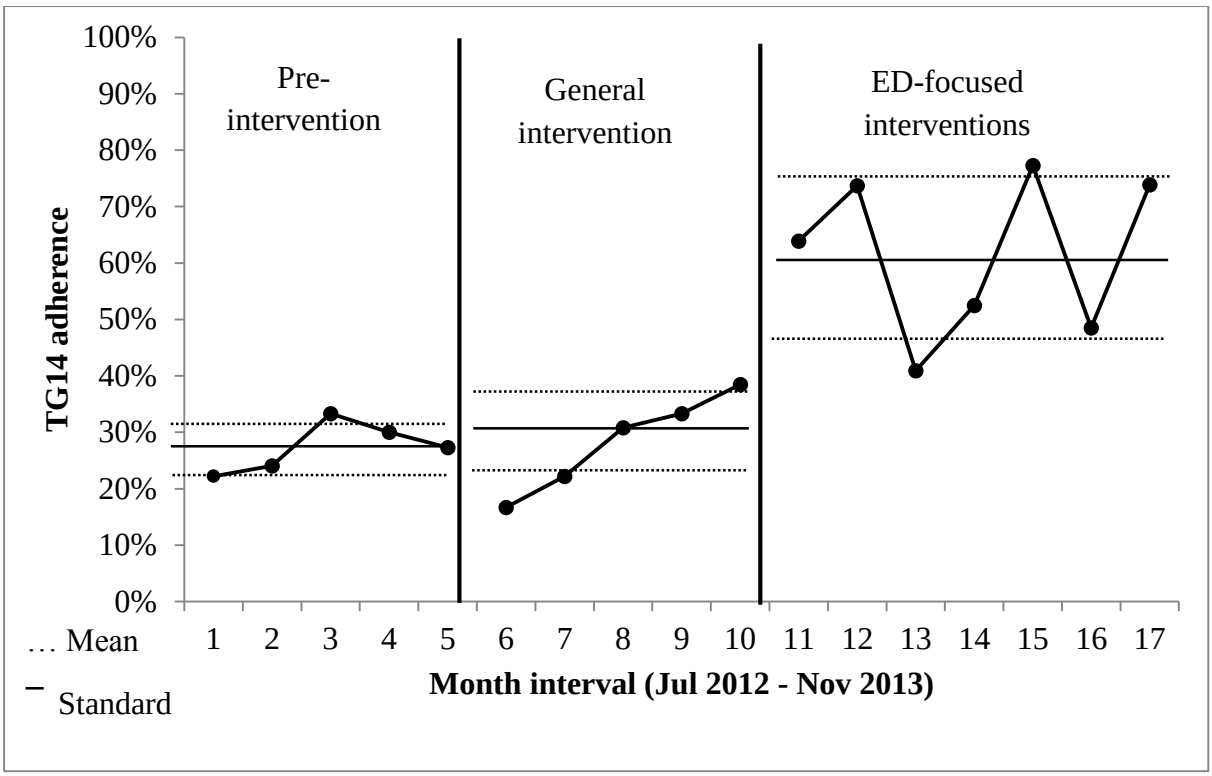


Figure 8.1: Impact of general and ED-focused interventions on the monthly rates of adherence to TG14 for CAP management at the RHH.

8.4. Discussion

A multifaceted intervention was delivered over a one-year period from December 2012 to November 2013, aiming to improve adherence to the recommendations in TG14 for the empirical management of CAP. After development of the local consensus guidelines based on TG14, the multifaceted intervention was implemented in two phases over successive time periods. The first was a general educational intervention, when all medical doctors were targeted, including ED physicians. The second phase was focused in the ED where a CAP clinical pathway was introduced and followed-up with monthly feedback to ED doctors regarding adherence to the guideline recommendations. Overall, the results showed that the ED-focused intervention significantly increased the guideline adherence rate when compared to pre-intervention and the general intervention.

It is recognised that there can be several barriers impairing medical staff adherence to guidelines (151). Therefore, to overcome these barriers, multifaceted intervention strategies were utilised in this study. To enhance adoption to the recommended guidelines, active implementation of guidelines has been strongly recommended (117, 129, 130). One of the active strategies, which has been considered essential to enhance guideline adherence, is the involvement of key local opinion leaders in the development and implementation of local guidelines that are broadly consistent with the latest version of national guidelines (117, 129). In our study, this involvement occurred from the earliest stages in the development of local CAP guidelines and continued through to their final approval and implementation.

During the general intervention phase, a multifaceted educational approach was utilised. However, our data indicate this had no significant impact on adherence to the guidelines. This is consistent with previously published studies, which found educational interventions alone to have a limited impact (325, 327).

It has been reported that emergency departments receive minimal attention from antimicrobial stewardship teams compared to other hospital medical departments (333). However, the vast majority of CAP patients in Australian hospitals are initially seen and assessed by ED doctors and they invariably initiate empirical antibiotic therapy. So, it is logical to target this area for the initial management of CAP. During the ED-focused intervention, a clinical pathway was introduced in the ED and this was followed-up with monthly feedback about antibiotic prescribing practices for the management of suspected CAP in the ED.

In a Cochrane review of 140 studies looking at the impact of audit and feedback on practice, a wide variation in impact was noted, ranging little or no effect through to a large effect (326). The authors concluded that the impact of audit and feedback is largely dependent on the format, source and frequency of the delivered feedback. For example, the author suggested that the maximum effect of this strategy might be achieved if the person responsible for the feedback has authority or is a senior colleague (compared to a researcher), and the feedback is delivered at least monthly in written and verbal forms. In our study, the selected patient profiles were reviewed and reported by the hospital antimicrobial stewardship team on a monthly basis and were sent to the head of the ED department for distribution to ED doctors. Moreover, a clear clinical pathway for CAP including diagnosis, severity assessment and recommended antibiotic therapy had been introduced to the ED, aiming to standardise each of these components to reduce the chance of non-adherence to guidelines. In their meta-analysis of 27 studies looking at the impact of clinical pathways on clinicians' practice and patient clinical outcomes, Rotter *et al.* reported that the use of clinical pathways was significantly associated with reduced in-hospital complications and increased documentation in medical notes (358). A number of studies have found that implementation of clinical pathway for the management of CAP provide positive impacts in terms of clinical outcomes and process of

care (268, 359-361). In a retrospective study of 22,196 patients admitted with CAP to 31 tertiary hospitals, Hauck *et al.* reported that patients who were placed on the CAP clinical pathway were less likely to die than those who were not (OR = 0.37; 95% CI , 0.2- 0.7) (359). Conversely, a Canadian multicentre controlled study of 1743 patients with CAP in 19 teaching and community hospitals, could not indicate any significant difference in terms of patients' clinical outcomes between a CAP clinical pathway and non-clinical pathway hospitals (268). However, the study showed an 18% reduction in the admission for mild CAP patients in those hospitals who were managed with the clinical pathway (31% vs 49%; $p < 0.05$). Furthermore, this study reported that hospitals using the clinical pathway were more likely to prescribe a single antibiotic when compared to the non-clinical pathway hospitals (64% vs 27%; $p < 0.001$).

Junior doctors appear to play an important role in the empirical management of CAP in the ED. As the study site is a teaching institution, it is more likely that the first-line medical staff involved in management of CAP will be less-experienced. This was supported by the large drop in guideline adherence rates during July and October 2013, when three-month junior doctor rotations began. Adjustment to the new department's rules and expectations at the beginning of the rotation might be challenging for junior doctors (320). During the first weeks of the rotation, junior doctors are more likely to be influenced by the prescribing habits of their seniors, and less influenced by guidelines (295). It is therefore crucial to target both senior and junior doctors when wishing to implement a change in practice.

The ED is one of the busiest hospital departments, with a requirement for rapid clinical decision making, which may impact on assessment and prescribing. Therefore, a CAP clinical pathway could serve to provide useful direction to junior medical staff, when it is difficult to consult senior colleagues within a short timeframe. Auditing and feedback provided a valuable opportunity to enlighten new and existing ED medical staff about the presence of the

guidelines and clinical pathway in their department, together with communicating the hospital's expectation that these will be used.

8.5. Limitations

A number of limitations regarding this study should be acknowledged. This was a retrospective study which measured adherence to guideline recommendations and it is acknowledged that clinical judgment might be required to apply the guidelines when assessing and prescribing for patients with CAP. However, the aim of this study was to assess the changes toward the desired prescribing behaviours for the management of CAP and this factor applies equally to both pre- and post-intervention phases. Moreover, our study was conducted in a single teaching hospital; therefore, other multi-site studies in hospitals with different systems are required to ensure generalisability of our findings.

8.6. Conclusion

An ED-focused intervention including the introduction of a clinical pathway for CAP management and monthly feedback was a successful strategy to improve adherence to the CAP guideline recommendations. On the other hand, relying on a multifaceted educational intervention alone failed to improve adherence in the timescale that we studied. Our findings suggest that focusing an intervention to improve CAP management at the ED, with clear communication of the desired management practice via a CAP clinical pathway, coupled with regular feedback, is a preferable approach.

Chapter 9. Evaluation of empirical ceftriaxone prescribing at the RHH

9.1. Introduction

Several clinical practice guidelines have been developed in an attempt to improve antibiotic prescribing (144, 182, 183, 186, 362). The main aims of these are to promote timely commencement of treatment and minimise unnecessary use of broad-spectrum antibiotics, such as ceftriaxone, thereby assuring effective therapy whilst reducing unnecessary resistance and unintended side effects, such as CDI, which might be associated with poor clinical outcomes and increased healthcare costs (66, 69, 73, 363, 364).

Several studies have reported an association between ceftriaxone consumption and the incidence of CDI in the hospital environment (31, 365, 366). For instance, in one British study, it was found that changing the hospital policy by replacing cefotaxime with ceftriaxone for the empirical management of CAP led to an increase in ceftriaxone use by 35%, which was associated with a significant increase in CDI incidence (367). A possible explanation for these findings may be that ceftriaxone is excreted in high concentration in bile, which would lead to extensive distortion of anaerobic bacteria that are associated with CDI (368). Conversely, it was found that restricting the use of ceftriaxone was associated with reduced incidence of CDI (369-371). As a result, the British Thoracic Society does not recommend ceftriaxone as a first-line therapy, even for those patients with severe CAP (186). This recommendation was supported by other reports showing a decreased incidence of CDI when ceftriaxone use was restricted (367).

Additionally, it has been shown that the consumption of ceftriaxone is linked with an increased incidence of resistant pathogens such as *extended-spectrum beta-lactamases* (ESBLs) producing bacteria, *methicillin-resistant Staphylococcus aureus* (MRSA), and

vancomycin-resistant Enterococcus (VRE) (306, 372, 373). Bloodstream infections caused by VRE are one of the specific life-threatening nosocomial infections that have been linked with the use of ceftriaxone. (306) While the use of extended-spectrum cephalosporins generally is considered a risk factor for the emergence of resistant nosocomial pathogens, the high biliary concentration of ceftriaxone is thought to explain the particularly strong association between use of this drug and the emergence of VRE .(306)

These reasons, coupled with the fact that it is one of the most commonly prescribed antibiotics in Australian hospitals, make it important to evaluate the appropriateness of ceftriaxone prescribing. For instance, third-generation cephalosporins, including ceftriaxone, represented almost half of the antibiotics prescribed in the ED for the management of lower respiratory tract infections (374). However, it has been shown that in almost half of cases ceftriaxone was prescribed inappropriately when assessed against the recommendations in TG14 (168). Consequently, improved concordance with TG14 would be expected to lead to more appropriate ceftriaxone prescribing.

To help inform initiatives to promote improvements in ceftriaxone prescribing, this study aimed to:

1- Characterise the empirical prescribing of ceftriaxone at the RHH and to assess concordance with the recommendations of TG14 for each indication over two time periods (before and after the initiation of the intervention).
2- Examine the association between the hospital's ceftriaxone consumption and the incidence of hospital-identified CDI during the study periods.

9.2. Methods

9.2.1. Ceftriaxone usage and concordance with TG14

Inclusion and exclusion criteria

All patients ≥ 18 years old who received ceftriaxone therapy in two time periods, 1 January to 31 March 2012 (Period 1) and 1 April to 31 June 2013 (Period 2), were included in this study. When a patient received a course of ceftriaxone-based therapy more than once (whether due to readmission or due to other indications during one hospital stay), only the treatment associated with the first indication/admission was included in the study. Patients receiving ceftriaxone were identified in two ways. Firstly, the pharmacy department at the RHH provided a list of all inpatients for whom ceftriaxone had been dispensed. Secondly, because ceftriaxone is supplied by pharmacy as a stock item to the ED, the medical records of all patients who presented in the ED were screened to identify those who received ceftriaxone.

Patients, who received ceftriaxone for prophylaxis (medical or surgical) or directed therapy, where the causative organism had been identified, were excluded. All other cases were considered to have received empirical therapy.

Data collection

Digital medical records were utilised to examine patients' files. For ceftriaxone regimens, drug charts were screened to obtain information including dose, frequency, time of administration, course duration and penicillin allergy status. Doctors' notes were screened to obtain principal indications, any prior antibiotic use, clinical examination, laboratory results, and patients' characteristics.

Outcomes measurement

Ceftriaxone use was considered to be appropriate for patients with a documented indication for which ceftriaxone is the first-line empirical therapy in TG14 (Table 9.1). In cases where ceftriaxone was recommended only in the presence of penicillin allergy, ceftriaxone was considered to be appropriate for those patients with a documented penicillin allergy, except where this was noted to be an immediate hypersensitivity reaction. In cases where gentamicin was the recommended first-line therapy, ceftriaxone was only considered to be appropriate for patients with pre-existing hearing and vestibular problems, which are accepted contraindications to aminoglycoside therapy. For patients with CAP, the appropriateness of ceftriaxone was assessed based on the severity, as per TG14.

Table 9.1: Indication for empirical use of ceftriaxone as per TG14.

Site of infection	Infectious disease
Respiratory tract infections	• Acute epiglottitis • Moderate to severe hospital acquired pneumonia • Severe community acquired pneumonia • Moderate community acquired pneumonia if non-immediate penicillin allergy
Intra-abdominal infections	• Ascending cholangitis or acute cholecystitis where gentamicin is contraindicated or non-immediate penicillin allergy • Severe diverticulitis if non-immediate penicillin allergy • Acute hepatic encephalopathy (unidentified precipitant) • Severe necrotising pancreatitis if non-immediate penicillin allergy • Peritonitis due to perforated viscus if non-immediate penicillin allergy • Spontaneous bacterial peritonitis
Urinary tract infections	• Acute pyelonephritis where gentamicin is contraindicated
Central nervous system infections	• Brain abscess or subdural empyema • Epidural abscess where gentamicin is contraindicated or non-immediate penicillin allergy • Meningitis
Genital and sexually transmitted infections	• Sexually acquired infection • Epididymo-orchitis where gentamicin is contraindicated
Skin and soft tissue infections	• Bites and clenched fist injuries (established infection)
Cardiovascular system infection	• Infected aneurysms and intravascular prostheses
Eye infections	• Orbital cellulitis

9.2.2. Association between ceftriaxone consumption and hospital identified CDI

Data collection

To identify whether there was an association between ceftriaxone consumption and the incidence of hospital identified CDI, data for these variables were examined for the period January 2012 to June 2013. Ceftriaxone consumption data, in terms of grams per quarter, were obtained from the RHH's pharmacy department. Data about the number of hospital-identified CDI cases per quarter was obtained from the Tasmanian Infection Prevention and Control Unit (375).

9.2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. Chi-square and Fisher's exact tests were used to test the significance between categorical data. Fisher's exact test was used if one of the expected values had less than five patients or events. To compare categorical and scale data, the Mann-Whitney U test was used. To compare continuous data a student t-test were utilised. P-value of < 0.05 was considered statistically significant.

9.2.4. Ethical approval

Ethics approval was granted by the Tasmania Health and Medical Human Research Ethics Committee [Ref no. H0012489].

9.3. Results

9.3.1. Ceftriaxone usage and concordance with TG14

Ceftriaxone was administered to a total of 299 and 355 patients at the RHH during study periods 1 and 2 respectively. Of these, 54 patients (18.1%) and 72 patients (20.3%) were excluded during periods 1 and 2 respectively, the reasons for this are summarised in Table 9.2.

Table 9.2: Reason for exclusion from the study.

Exclusion criteria	Period 1	Period 2
Directed therapy	32	41
Prophylaxis	22	31

Patients' characteristics

Patient characteristics in the two study periods were similar and are summarised in Table 9.3. The only parameter where there was a significant difference between the study periods was the length of stay (LOS) which was longer in period 2.

Table 9.3: Patients' characteristics.

Patients' characteristic	Period 1 N = 245	Period 2 N = 283
Gender; male	121 (49.3)	158 (56)
Age (years); median (range; percentile quarter 25th – 75th)	66 (18 - 95; 50 - 77)	66 (18 – 98; 47 – 78)
Allergic to penicillin	38 (15.5)	47 (16.7)
Estimated glomerular filtration rate (mL/min/1.73m^2)	68.8 ± 24.5	68.5 ± 24
Prior antibiotics within 7 days	17 (6.9)	14 (5)
Death during admission	22 (9)	20 (7.1)
LOS (days); median (range; percentile quarter 25th – 75th) [a]	5 (0-139; 3-9)	6 (0 – 137; (3 – 12)

Data presented as number (%) for categorical variables and mean ± standard deviation for numerical variables unless otherwise stated.
[a] The result is significant at the $p = 0.05$ level.

Ceftriaxone prescribing profile

Respiratory tract infections (RTIs), intra-abdominal infections and sepsis were the most common reasons for the empirical prescribing of ceftriaxone in both time periods (Figure 9.1). There was no significant difference between the two groups in terms of infection site profiles.

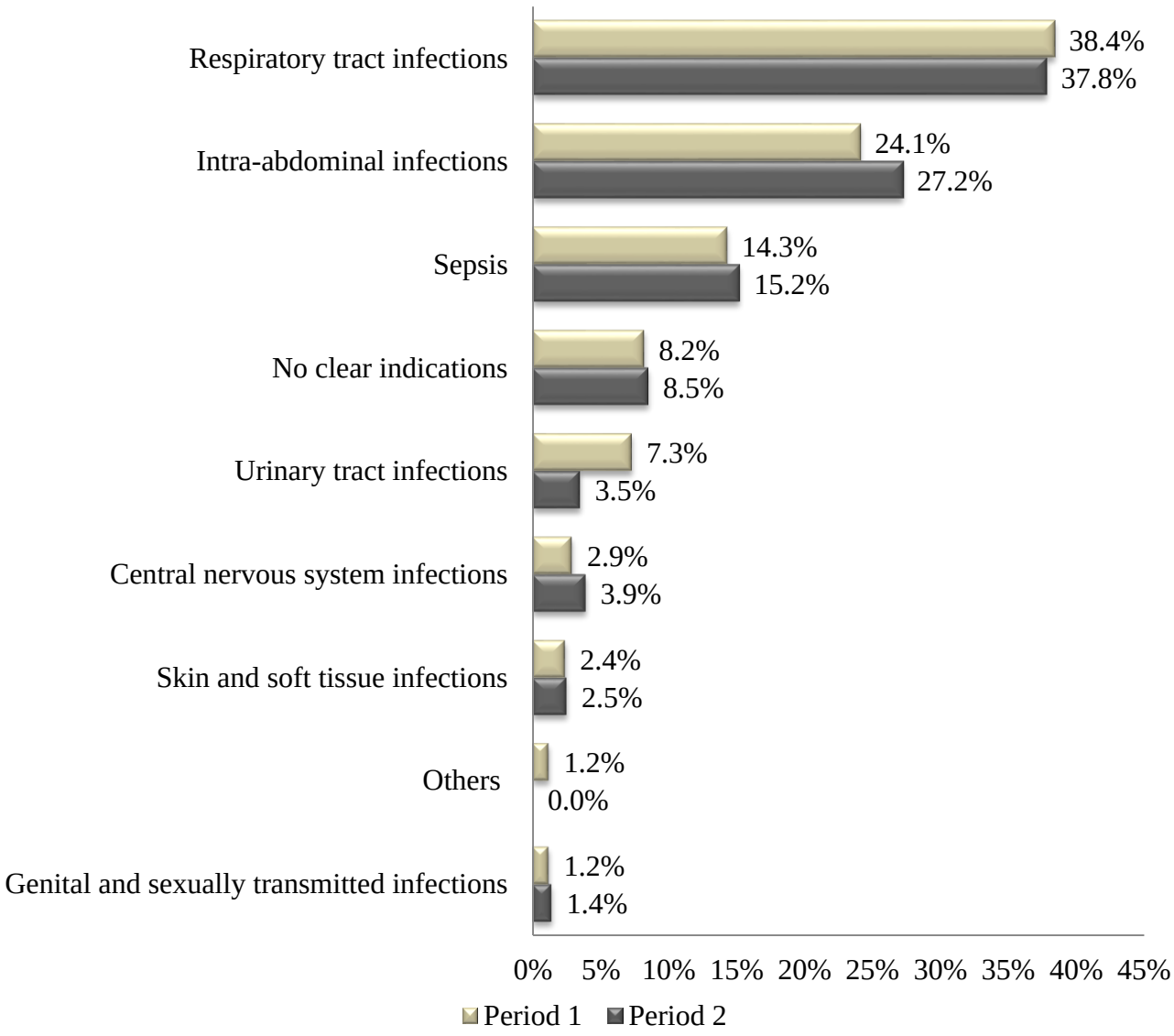


Figure 9.1: Ceftriaxone prescribing rates by site of infections during period 1 (n = 245) and period 2 (n = 283).

As can be seen from Table 9.4, CAP represented the majority of RTI cases where ceftriaxone was prescribed, accounting for 54.3% and 56.1% in the first and second periods, respectively. Within those infections classified as intra-abdominal, cholangitis, appendicitis and diverticulitis represented the main reasons for prescribing ceftriaxone in each time period. For septic patients, the source of sepsis was unknown for the majority of cases where ceftriaxone was prescribed; 54.3% and 60.5% for the first and second period, respectively.

Table 9.4: Empirical prescription of ceftriaxone within sites of infections.

Site of infection	Infectious disease	Period 1 N (%)	Period 2 N (%)
Respiratory-tract infections	**CAP** [a]	51 (54.3%)	60 (56.1%)
	HAP [a]	14 (14.9%	26 (24.3%)
	AECOPD [a]	12 (12.8%)	2 (1.9%)
	sinusitis	2 (2.1%)	2 (1.9%)
	Aspiration pneumonia	5 (5.3%)	2 (1.9%)
	Lung abscess	1 (1.1%)	-
	Pneumonia (immunocompromised) [b]	6 (6.4%)	12 (11.2%)
	Tonsillitis	1 (1.1%)	1 (0.9%)
	Pneumonia (fibrosis)	1 (1.1%)	-
	Pulmonary oedema	1 (1.1%)	-
	Ear infections	-	2 (1.9%)
	Total	94	107
Intra-abdominal infections	**Cholangitis**	14 (23.7%)	16 (20.8%)
	Appendicitis	9 (15.3%)	19 (24.7%)
	Diverticulitis	9 (15.3%)	16 (20.8%)
	Cholecystitis	8 (13.6%)	12 (15%)
	Hepatic encephalopathy (unknown source)	6 (10.2%)	-
	Pancreatitis	3 (5.1%)	-
	Peritonitis	3 (5.1%)	3 (3.9%)
	Hepatic encephalopathy (SBP) [a]	2 (3.4%)	2 (2.6%)
	Gastroenteritis	2 (3.4%)	1 (1.3%)
	Ulcerative colitis	2 (3.4%)	6 (7.8%)
	Duodenitis	1 (1.7%)	-
	Liver abscess	-	1 (1.3%)
	Small bowel obstruction	-	1 (1.3%)
	Total	59	77

Sepsis	**Unknown source**	19 (54.3%)	26 (60.5)
	Urinary	11 (31.4%)	10 (23.3%)
	Abdominal	2 (5.7%)	5 (11.6%)
	Respiratory	2 (5.7%)	-
	Skin	1 (2.9%)	2 (4.6%)
	Total	35	43
Urinary tract infections		18	10
No clear indication		20	24
Central nervous system infections	**Meningitis**	5 (71.4%)	10 (90.9%)
	Encephalitis	2 (28.6%)	1 (9.1%)
	Total	7	11
Skin and soft tissue infections	**Cellulitis**	4 (66.7%)	3 (42.9%)
	Wound infections	2 (33.3%)	3 (42.9%)
	Scrotal abscess	-	1 (14.3%)
	Total	6	7
Genital and sexually transmitted infections	**Epididymo-orchitis**	2 (66.7%)	1 (25%)
	Pelvic inflammatory diseases	1 (33.3%)	2 (50%)
	Scabies	-	1 (25%)
	Total	3	4
Others	**Iliopsoas collection**	1 (33.3%)	-
	Tooth abscess	1 (33.3%)	-
	Postpartum infection	1 (33.3%)	-
	Total	3	0

[a] Abbreviations are as follow: CAP "Community-Acquired Pneumonia"; HAP "Hospital-Acquired pneumonia"; AECOPD " Acute Exacerbation of Chronic Obstructive Pulmonary Disease"; SBP " Spontaneous Bacterial Peritonitis".

[b] Immunosuppressed patients are those patients who met at least one of the following criteria: (i) chronic use of prednisolone, (ii) had received chemotherapy within 3 month, (iii) on any other immunosuppressive agents for the management of solid organ transplantation or, and (iv) HIV positive.

Ceftriaxone dosing and site of administration

Within 24 hours of commencing ceftriaxone, 41 (16.3%) and 45 (15.9%) patients received more than one gram of ceftriaxone in periods 1 and 2, respectively (Table 9.5). Doses greater than one gram were more likely to be initiated in ED rather than non-ED units during the first study period ($p < 0.05$). However, no significant differences were found during period 2. In both study periods younger patients (< 65 years old) were more likely to receive a ceftriaxone dose exceeding 1g/day ($p < 0.05$).

Table 9.5: Patients who received more than 1 gram of ceftriaxone within the first 24 hours, by site of infection.

Site of infection	Period 1 (n = 245)	Period 2 (n = 283)
Respiratory tract infections [a]	13 (5.3%)	11 (3.9%)
Intra-abdominal infections	3 (1.2%)	6 (2.1%)
Sepsis	11 (4.5%)	11 (3.9%)
No clear indications	3 (1.2%)	5 (1.8%)
Urinary tract infections	-	1 (0.4%)
Central nervous system infections	6 (2.4%)	9 (3.2%)
Skin and soft tissue infections	2 (0.8%)	2 (0.7%)
Others	2 (0.8%)	-
Genital and sexually transmitted infections	-	-

[a] The result is significant at the $p = 0.05$ level.

Treatment duration with ceftriaxone

The median duration of ceftriaxone courses was two days (range = 1 – 11; IQR = 2 – 4) during period 1 and three days (range = 1 – 17; IQR = 2 – 4) in period 2. This difference is significant at the $p = 0.05$ level. As shown in Figure 9.2: Treatment duration of ceftriaxone during period 1 and 2., the majority of patients received ceftriaxone for three days or less during both the first (69.3%) and second periods (63.6%). Ceftriaxone-based therapy was altered in 94 (38.4%) and 70 (24.7%) patients after the first 24 hours of the initial administration during periods 1 and 2, respectively ($p < 0.05$). Ceftriaxone therapy was more likely to be ceased within the first 24 hours if it was initiated in the ED compared to non-ED units ($p < 0.05$); this was true for both time periods.

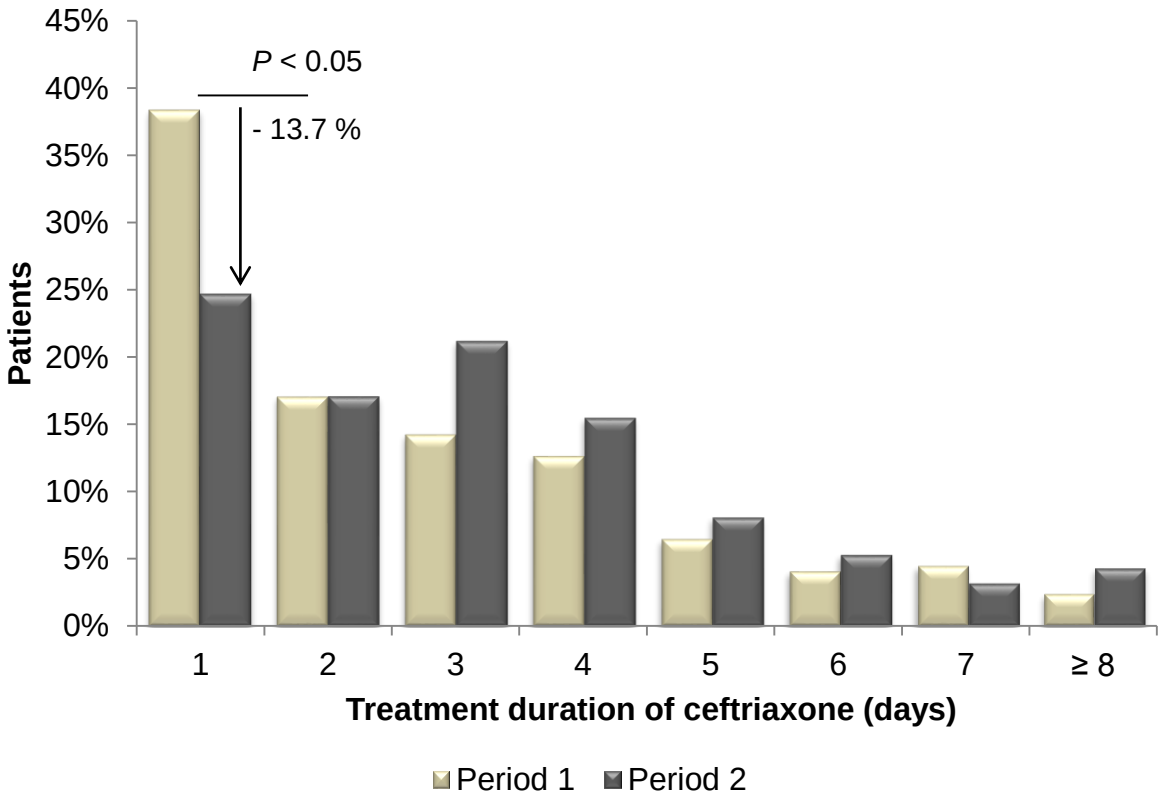


Figure 9.2: Treatment duration of ceftriaxone during period 1 and 2.

Concordance with TG14

The ceftriaxone prescribing based on the indication, as per TG14, in the two groups are shown in Table 9.6. Ceftriaxone was considered appropriate in just 68 (27.8%) cases during study period 1 and 91 (32.2%) cases in period 2. The chi-square test did not show any significant differences between the two groups at $p = 0.05$ level.

Table 9.6: First-line and alternative indications of ceftriaxone as per TG14.

Indication	Period 1	Period 2
First-line therapy n (%)	56 (22.9%)	73 (25.8%)
Alternative therapy n (%)	88 (35.9%)	99 (35%)
Eligible n (%)	12 (13.6% out of 88)	18 (18.2% out of 99)
Not indicated n (%)	81 (33.1%)	87 (30.7%)
No clear indication	20 (8.2%)	24 (8.5%)

The comparative rate of TG14 concordant ceftriaxone use according to the infection site between the two study periods is shown in Table 9.7. Concordance to the TG14 for all indications, with the exception of RTI, was similar between the two study periods. For the RTI, concordant use of ceftriaxone significantly increased from 50% during the first period to 64.5% during the second study period ($p < 0.05$).

Table 9.7: Concordant indications of ceftriaxone with TG14, by site of infection.

Site of infection	Period 1 (n = 245)	Period 2 (n = 283)
Respiratory tract infections [a]	47/94 (50%)	69/107 (64.5%)
Intra-abdominal infections	14/60 (23.3%)	10/82 (12.2%)
Sepsis	2/32 (6.3%)	0/42 (0%)
No clear indication	0/20 (0%)	0/22 (0%)
Urinary tract infections	0/21 (0%)	1/22 (9.1%)
Central nervous system infections	5/7 (71.4%)	11/11(100%)
Skin and soft tissue infections	0/6 (0%)	0/6 (0%)
Others	0/3 (0%)	-
Genital and sexually transmitted infections	0/2 (0%)	0/2 (0%)

[a] The result is significant at the $p = 0.05$ level.

Ceftriaxone prescribing for community-acquired lower respiratory tract infections (CAP and AECOPD): subgroup analysis

During the first study period, 94 courses of ceftriaxone were prescribed for RTI. Of these, 63 (67%) courses were prescribed for either CAP or AECOPD. For those patients, ceftriaxone was only consistent with TG14 in 28 cases. During period 2, 107 courses of ceftriaxone were prescribed for RTI. Of these, 62 (57.9%) were prescribed for CAP or AECOPD and of these, prescribing was concordant with TG14 in 42 (67.8%) cases. The differences in ceftriaxone prescribing for these infections between period 1 and period 2 are highlighted in Table 9.8.

As the table shows, there was an increase in ceftriaxone prescribing for patients with moderate and severe CAP during the second study period. However, none of these differences were statistically significant. Interestingly, ceftriaxone prescribing was observed to be less likely to be given to patients with mild CAP and AECOPD during the second period. The results are significant at the $p = 0.05$ level.

Table 9.8: Empirical management with ceftriaxone and concordance with TG14 for the management of patients with community-acquired lower respiratory tract infection.

Concordance	Infectious disease	Period 1 (n = 63)	Period 2 (n = 62)
Concordant Indications	Severe CAP	21 (33.3%)	31 (50%)
	Moderate CAP: documented penicillin allergy	7 (11.1%)	11 (17.7%)
Discordant indications	Moderate CAP: no documentation of penicillin allergy	11 (17.5%)	16 (25.8%)
	Mild CAP [a]	12 (19%)	2 (3.2%)
	AECOPD [a]	12 (19 %)	2 (3.2%)

[a] The result is significant at the $p = 0.05$ level.
The patients were assigned to a severity group based on the TG14 severity scoring system as shown in Figure 2.1.

9.3.2. Association between ceftriaxone consumption and hospital-identified CDI

Figure 9.3 illustrates the identified rates of CDI and the volume of ceftriaxone consumed at the RHH between January 1st 2012 and June 30th 2013. The mean consumption of ceftriaxone 1 gram vials was 2003.2 per quarter. The mean rate of hospital-identified CDI was 8 cases per 10 000 patient days. Overall, there was no obvious association between the hospital consumption of ceftriaxone and the rates of hospital-identified CDI ($p > 0.05$).

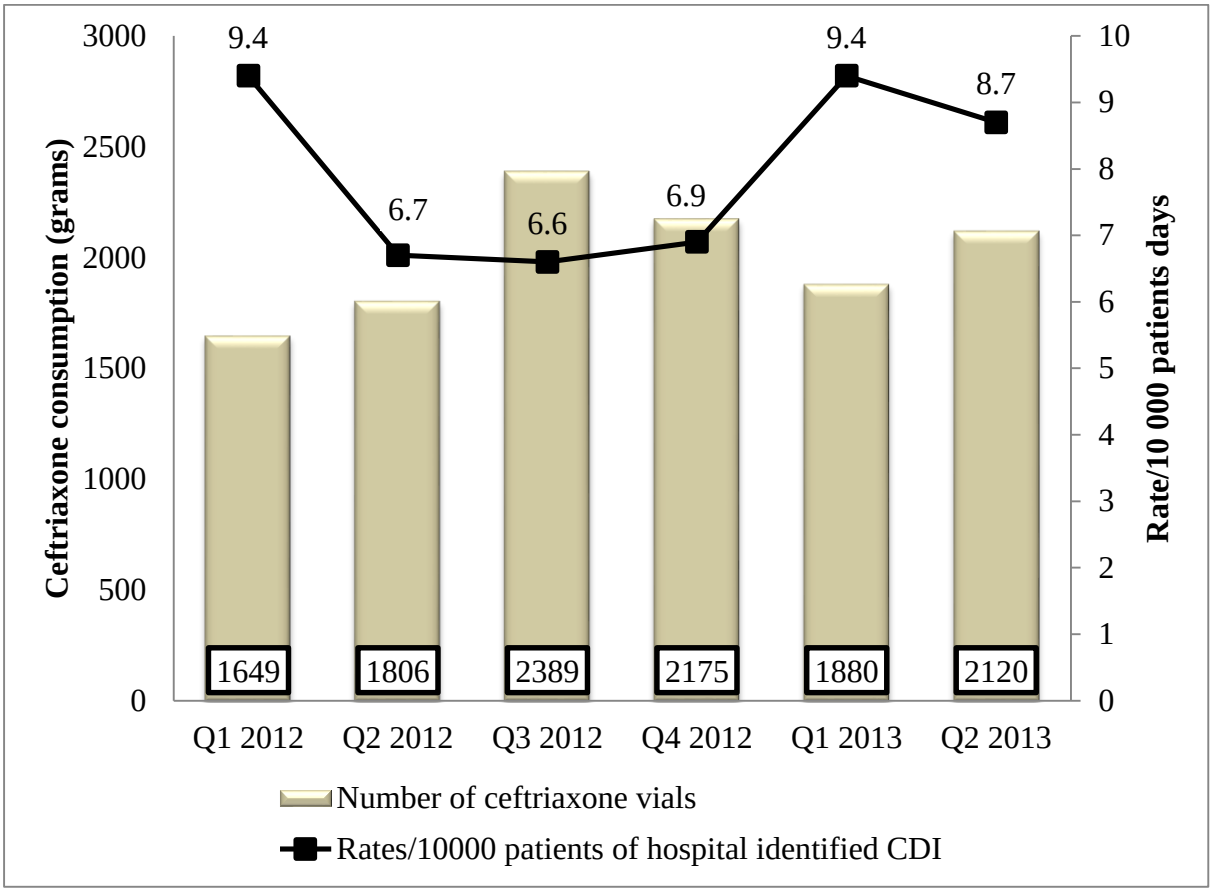


Figure 9.3: Number of ceftriaxone vials (1 gram) and rate of RHH identified CDI per 10 000 patient days by quarter.

9.4. Discussion

The current study has two main findings. First, it was clear that ceftriaxone was often prescribed outside TG14 recommendations. Second, this study has demonstrated that ceftriaxone prescribing for the management of patients with RTI was improved significantly in the second study period during the multifaceted intervention to improve the management of adult patients with CAP.

Our finding demonstrated that ceftriaxone prescribing is frequently inconsistent with guidelines is in line with a previous Australian study. Conducted in the late 1990s in 51 Victorian hospitals, compliance with national guidelines regarding use of third-generation cephalosporin drugs was almost identical to that found in this study (167). However, after more than a decade, and despite the implementation of antibiotic stewardship programs in many Australian hospitals (117), empirical prescribing of ceftriaxone frequently remains inappropriate.

Most patients who received ceftriaxone presented with RTI, with the majority of these being diagnosed with CAP. It was shown in one Australian study that more than 30% of patients with non-severe CAP received ceftriaxone as an empirical therapy in the ED (374), when ceftriaxone is only indicated to be used as a first-line treatment in severe cases. This problem has led to national initiatives to improve the adherence to the CAP guidelines in hospitals around Australia. However, only modest improvement has been seen; despite the educational programs, ED doctors continue to prescribe ceftriaxone for patients with mild CAP, and for patients with moderate CAP where there is no documented allergy to penicillin (250).

In one of the largest Australian studies looking at causative pathogens in CAP, *Streptococcus pneumoniae* was responsible for the vast majority of cases (210).

Consequently, the empirical use of narrower spectrum antibiotics could be as effective as the broader spectrum antibiotics for many cases of CAP, but carry a lower risk of both CDI and promoting the emergence of drug-resistant organisms.

With respect to ceftriaxone dosing, around 16% of the study population received more than one gram of ceftriaxone within the first 24 hours of therapy. Most of these cases were RTIs and sepsis. In these cases, when ceftriaxone is indicated, the TG14 recommended dose of ceftriaxone is one gram daily. It has been shown that two grams of ceftriaxone has no superiority over the one gram regimen for the management of moderate to severe CAP (376). For patients with sepsis, increased volume of distribution of antibiotic is a common phenomenon, requiring higher than usually recommended dose. However, the likelihood of a one gram ceftriaxone regimen producing serum concentrations below the minimum inhibitory concentration after twenty-four hours is low for common bacterial pathogens, even in severely ill septic patients (377). It is also worth noting that patients in the second period were significantly less likely to receive more than one gram of ceftriaxone initially. It seems possible that this result is due to the intervention to improve CAP management where the recommended dose is one gram/day.

In terms of ceftriaxone duration, it has been shown that the median duration of ceftriaxone administration was significantly longer than that seen in the first period (2 days vs 3 days, $p < 0.05$)). Since most of the patients who received ceftriaxone did so for CAP, it is likely that more patients in the second period were correctly classified as having severe CAP and ceftriaxone might be assumed to be the appropriate antibiotic for those patients during the second and third days. This assumption was supported by a significant decrease in rate of ceftriaxone cessation during the first day in the second study period compared to the first, which might suggest that more cases in the first period were inappropriately initiated with ceftriaxone.

Another important finding from the study was a significant improvement in the adherence to the recommended guidelines with regard to the ceftriaxone usage for the management of RTI during the second period since the second study period coincided with the multifaceted intervention to improve CAP management, we could not ignore the influence of the intervention on the overall improvement of ceftriaxone usage for patients with RTI. Among patients with mild community-acquired lower respiratory tract infections (CAP and AECOPD), ceftriaxone prescribing was significantly reduced consistent with TG14. While the lower prescribing of ceftriaxone in period 2 could be explained by the hospital's intervention to improve CAP management, it was interesting that the prescribing of ceftriaxone was also reduced in AECOPD. This may however be related to the intervention for CAP. The emphasis on the accurate diagnosis of pneumonia might lead to less ceftriaxone prescribing when the change in chest X-ray was not evident, as the TG14 does not recommend the use of ceftriaxone for patients with AECOPD unless a diagnosis of CAP is confirmed. There was a 16.7% increase in ceftriaxone prescribing for severe CAP during the second study period, which would be consistent with greater concordance with TG14, however this did not reach statistical significance.

During the intervention for CAP management, one of the key messages was to highlight the relationship between the misuse of ceftriaxone and the emergence of pathogens resistant, to antimicrobials. However, our intervention showed no effect on ceftriaxone prescribing other than for RTI. The results from this study might suggest that to improve ceftriaxone prescribing more widely, an intervention across all hospital departments is required.

Studies found that despite doctors' awareness of the direct relationship between excessive use of broad-spectrum antibiotics and the rise in antibiotic resistance (378, 379), there may be factors that lead them to prefer using ceftriaxone empirically. The first could be a suspicion of multiple infection sites as reported in chapter 3 when ED doctors were

interviewed about factors affecting their ceftriaxone prescribing. For this reason, doctors might choose ceftriaxone with its broad spectrum in order to cover the most likely pathogens in multiple body sites. TG14 only provides recommendations for the management of infectious diseases in single body systems and not for those with clinical presentations that may reflect multiple sites. However, it is also possible that insufficient education about infectious diseases in medical school might also lead to misuse of antibiotics, especially by inexperienced junior doctors (380, 381). Other possible factors include lack of awareness of or disagreement with some of the antibiotic guidelines' recommendations (300).

Contrary to expectations, this study has been unable to demonstrate the relationship between ceftriaxone consumption and CDI incidence at the RHH. However, it is important to bear in mind that the risk of CDI is multifactorial. Those risk factors might relate to medications or patients' characteristics. Medications that have been shown to be associated with an increased incidence of CDI include proton pump inhibitors (382, 383), histamine receptor blocker (383, 384), and other broad-spectrum antibiotics, such as fluoroquinolones (385, 386). Risk factors for CDI related to patients characteristics include leucocytosis (white blood cell count > 13,000 cells per millilitre) and hypoalbuminaemia (serum albumin < 2.7 milligrams per decilitre) (383). Furthermore, previous admission within 60 days, obesity, severe disease and increasing age also considered as independent factors that have been shown to increase the risk of being infected with CDI (387-390). On the other hand, studies show that some factors might protect against CDI. For example, it has been shown that patients who used statin prior to hospital admission are less likely to be infected with CDI than those who did not (391). Moreover, it has been shown that CDI incidences are less likely when patients receive doxycycline as part of ceftriaxone-based therapy when compared to those who received different ceftriaxone-based regimens (392).

9.5. Limitations

There are several limitations to this study that should be acknowledged. This was a retrospective study with a reliance on documentation in medical records. Also, post-surgical indications were excluded, since it was not clear whether the indication was for prophylaxis. Therefore, some post-surgical ceftriaxone usage for empirical purposes might have been missed.

With respect to ceftriaxone consumption and the incidence of CDI, the current study has only examined the effect of ceftriaxone on the CDI incidence rates; however, the study did not control other risk factors that might contribute in CDI, nor take into account cases of CDI that presented in the community following hospitalisation and receipt of ceftriaxone.

9.6. Conclusion

Ceftriaxone was often prescribed outside the recommendations in Therapeutic Guidelines. Most patients who received ceftriaxone presented with RTI, with the majority of these being diagnosed with CAP and receiving their first dose in ED. Furthermore, this study has shown that the multifaceted intervention to improve the management of CAP has impacted favourably on the overall use of ceftriaxone for patients with RTI, with reductions in use of ceftriaxone for mild AECOPD as well as CAP. Accordingly, interventions to improve the management of other infections might lead to overall reduction of ceftriaxone. Since most ceftriaxone courses were initiated in ED, efforts to improve the empirical use of ceftriaxone should include a focus on the ED. With respect to ceftriaxone consumption and the rates of CDI, our data failed to find any significant relationship. Future research should, therefore, take into account other risk factors associated with CDI.

Chapter 10. Conclusions and future recommendations

Non-adherence to guideline recommendations for empirical management of adults with CAP continues to negatively impact on attempts to improve the quality use of antibiotics in hospitals. The main goal of the current project was to implement and evaluate the impact of the selected interventions on the guideline adherence rates and patients' clinical outcomes. One of the most significant findings to emerge from this research project was the positive impact of the ED-focused intervention strategies, introduction of a CAP clinical pathway and monthly feedback to the prescribers on the adherence to CAP guidelines. The second major finding was a reduction of inappropriate ceftriaxone use for patients with non-severe CAP in the intervention group. The third major finding was the improvement in mortality rates and LOS, among patients in the intervention group compared to the non-intervention group. Before selecting and implementing the interventions' strategies, we conducted quantitative and qualitative studies to identify barriers that might hinder doctors from adhering to the guidelines. Furthermore, we conducted a survey among Australian hospitals in order to identify strategies that have been used to improve the empirical management of CAP and perceived as successful. The findings from these studies influenced our decision regarding intervention strategies. Taken together, these results suggest that tailoring interventions to identified barriers and enablers can significantly improve the adherence to CAP guidelines and patients' clinical outcomes as well as reducing the unnecessary use of ceftriaxone.

The findings from this project make several contributions to the current literature. It is the first Australian study that explores barriers to CAP guideline adherence and then uses these findings to influence the choice of intervention strategies. The investigation has also gone some way toward enhancing our understanding of factors that influence doctors to prescribe ceftriaxone empirically for the management of CAP in ED sitting. Furthermore, this

is the first Australian study reporting that improve adherence to CAP guidelines favourably impacts on clinical outcomes. Finally, the methods used to enhance adherence to CAP guidelines may be applied to other community-acquired infections where the initial hospital treatment is given in the ED, such as urinary tract and intra-abdominal infections. Additionally, these strategies might be generalised to other hospitals who share the same healthcare system.

Although this research project has successfully demonstrated that the intervention increased adherence to CAP guidelines and improved clinical outcomes, it has certain limitations in terms of that this intervention was only applied at one hospital.

This project indicates the need for further research to:

1- Confirm the association between guidelines adherence and clinical outcomes
2- Investigate the efficacy of tailored intervention compared with standard intervention, such as education sessions.
3- Further identify and characterise barriers to guideline adherence conducted.
4- Investigate the impact of the intervention on other outcomes, such as readmission rates, treatment failures, time to clinical stability and ICU admission.
5- Determine if the impact of the Clinical CAP pathway with monthly feedback can be reproduced in other hospitals in order to help to confirm that these strategies are effective tools for AMS teams to use
6- Assess the long-term effect of the intervention
7- Investigate the effect of the same intervention strategies on other common infections

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Appendices

Appendix A. CAP Auditing tool.

Community Acquired Pneumonia (CAP) auditing tool

1. Patient study number: _____ 2. Hospital code: _____

3. Age: *Patient MUST be ≥ 18 years old.*

4. Gender: male female 4a. If female: Pregnant? Not Yes

Breast- Not Yes

5. Was a history of an adverse drug reaction to penicillin documented? No Yes (specify_____

5a. Were any other previous adverse reaction(s) to antibiotics No Yes (specify_____

6. Date of admission to RHH: DD / MM / YY 6a. Admitted via ED? No Yes

7. Admitted to RHH from: Home Nursing Home Hostel Another ED Other

8. Medical history

9. If the patient was admitted were there other factors that may have contributed to the admission? Co-morbidities Unmet social need Other No

Failed outpatient therapy Oral intolerance Not applicable

10. Initial diagnosis (from doctor's notes): _____

11. Was evidence of opacity, consolidation or primary infiltrates No Yes Not documented No chest X-ray

12. Data required for the study

12a. Data required for SMART-COP and CORB

Signs on examination	***Record the first value***	
acutely altered mental state	Yes Not documented	
respiratory rate	_____ per min	Not documented
systolic blood pressure/ diastolic blood pressure	_____ mm Hg	Not documented
temperature	_____ °C	Not documented
pulse rate	_____ per min	Not documented
Confusion	Yes No	Not Documented

Results of investigations	***Record the first value***	
arterial / venous pH	_____	Not documented
serum urea	_____ mmol/L	Not documented
serum sodium	_____ mmol/L	Not documented
serum glucose	_____ mmol/L	Not documented
haematocrit (HCT)	_____ %	Not documented
paO_2	_____ mm Hg	Not documented
O_2 saturation	_____ %	Not documented
pleural effusion on CXR	Yes No	Not documented
Albumin	_____ g/L	Not documented
Multilobar CXR	Yes No	
Scoring method	AMARTCOP CORB PSI CURB-65 Not documented Score……	
CAP pathway utilised	Yes No	Not documented

14. Was the use of antibiotics in the 7 days prior to attendance to the RHH documented? No Yes

If yes, please document antibiotic, route and indication:

Antibiotic	Dose	Route

15. Were antibiotics prescribed in the ED ? (include external scripts) No Yes

If yes, please document INITIAL ANTIBIOTIC REGIMEN:

Antibiotic	Dose	Frequency	Route

16. Details of antibiotics prescribed on the ward

17. Did the patient die during this admission? No Yes

18. Date of discharge from hospital or death^: DD / MM / YY ^if patient died no need to answer further questions.

19. Discharged from RHH to: Home Nursing home/hostel Another hospital

20. Diagnosis documented on discharge summary:

21. Was information on antibiotic therapy on discharge or follow-up appointments provided on discharge summary? No Yes

22. Was the patient readmitted within 14 days of discharge with a lower respiratory tract infection? No Yes Not documented

General comments:

e.g. Microbiological test results

Appendix B. Survey on the management of community-acquired pneumonia for medical staff at the RHH

UTAS FACULTY OF HEALTH SCIENCE School of Pharmacy

RHH ROYAL HOBART HOSPITAL

Survey on the management of community acquired pneumonia (CAP)

Dear Dr.

You are invited to take part in this survey regarding the empirical antibiotic management provided to patients diagnosed with CAP.

A recent study at the RHH has suggested that the empirical use of antibiotics for the management of CAP is often inconsistent with the Therapeutic Guidelines Antibiotic, version 14 (TG14).

The purpose of this questionnaire is to learn more about factors that may influence RHH doctors' decisions regarding antibiotic therapy for the management of patients with CAP and the appropriateness of the Therapeutic Guidelines' recommendations. **Filling out the survey should take less than three minutes.** An enclosed free envelope for you to return the survey is provided.

To thank you for your time we would like to provide you with a **cinema voucher** and summary of the results when available. To enable us to send the voucher and the feedback, please send this information sheet with your name and email address with the separate enclosed envelope provided. This is to ensure your anonymity when completing the survey.

Your responses to the survey will be totally confidential and anonymous. Information gained from this survey might be published or presented in a conference. However, no participant will be identifiable to any publication. This study has been reviewed and approved by the Human Research Ethics Committee (Tasmania) Network.

If you have any concerns regarding completing or participating in this survey, please feel free to contact Maher Almatar at 62261069, on extension 8535 or via e-mail at malmatar@utas.edu.au. If you have any concerns about any ethical issue regarding this project please contact Human Research Ethics Committee (Tasmania) Network (phone 03 6226 1956 or email: adele.kay@utas.edu.au).

This survey has been developed with the cooperation of the RHH Antimicrobial Stewardship Committee.

Your name:.....

Email address:..... **I would like to receive feedback on the study results** ☐

Thank you for your assistance

Yours sincerely,

Dr Tara Anderson

Infectious Disease Physician and Clinical Microbiologist; Medical Director of Infection Prevention and Control Unit; Royal Hobart Hospital

Mr Maher Almatar

PhD candidate, School of Pharmacy, Faculty of Health Science; University of Tasmania

This survey relates to the recommendations for management of CAP in adults outlined within the 2010 Therapeutic Guidelines Antibiotic (Antibiotic TG14).

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
A) I am familiar with the Antibiotic TG14 recommendations for the management of CAP in adults.	☐	☐	☐	☐	☐
B) In my workplace I have access to the Antibiotic TG14.	☐	☐	☐	☐	☐
C) I agree with the Antibiotic TG14 recommendations for the management of CAP.	☐	☐	☐	☐	☐
D) Why do you think that the Antibiotic TG14 is not always used by RHH doctors for the management of CAP? (Please answer all the questions)					
○ Doctors are unaware of the guideline.	☐	☐	☐	☐	☐
○ The guideline is not practical to implement.	☐	☐	☐	☐	☐
○ There is no time to refer to this guideline in practice.	☐	☐	☐	☐	☐
○ Guidelines interfere with doctors' professional autonomy.	☐	☐	☐	☐	☐
○ The guidelines are not sufficiently evidence based.	☐	☐	☐	☐	☐
○ The guideline is not clear.	☐	☐	☐	☐	☐
○ The RHH does not expect doctors to use the guideline.	☐	☐	☐	☐	☐
○ TG14 requires calculation of a severity score to choose antibiotics for CAP.	☐	☐	☐	☐	☐
○ Other guidelines exist for CAP management that conflict with TG14.	☐	☐	☐	☐	☐
○ Prescribing is largely under the direction of senior doctors.	☐	☐	☐	☐	☐

E) Which tool do you use to assess the severity of CAP?

PSI ☐ CURB65 ☐ SMARTCOP ☐ CORB ☐ No tool used ☐ Other (specify.....)

F) Ceftriaxone is not recommended for all cases of CAP. Why do you believe this is the case? (Please rank them by importance; 1 being most important and 6 being least).

Risk of cross-reaction with penicillin. ☐ Many cases are not severe. ☐

High cost. ☐ Risk of multi-drug resistance. ☐

Risk of *Clostridium difficile* infection. ☐ Penicillins give the same results in most cases. ☐

About me:

My position: Intern ☐ Resident ☐ Registrar ☐ Specialist/Consultant ☐
Other (specify.....)

My location: Emergency department ☐ Medical ☐ Surgical ☐ WACS ☐
Other (Specify.....)

Appendix C. Information sheet and consent form for the interviewees

USE OF CEFTRIAXONE FOR COMMUNITY ACQUIRED PNEUMONIA

Dear Dr .....,

The Unit for Medication Outcomes Research and Education (UMORE) at the School of Pharmacy, University of Tasmania would like to invite you to take part in a study examining the views of health professionals on the use of ceftriaxone for patients with Community-Acquired Pneumonia. This research is being undertaken as a component of Maher Almatar's PhD studies.

What will it involve?

Participation will involve an audio-recorded interview with Maher, either during normal business hours or after hours, whichever is convenient for you. For logistical reasons some of these interviews may need to take place over the phone. It is expected that these interviews will take approximately 30 minutes. To thank you for your time we would like to provide you with **a $50 gift voucher** at the end of the interview.

If you would like to take part, simply fill out the consent form attached and return it either by mail **(an enclosed free envelope for you to return the survey is provided)**, email (malmatar@utas.edu.au) or fax (03 6226 7627). All of the information that you provide will be carefully managed to protect your confidentiality. The audio-recorded interview will be labelled using a code number and in any reports or publications arising from this study only the combined results will be published. Although some verbatim quotes might be reported to illustrate the findings, they will be labelled using a pseudonym and edited to remove identifying information.

If you have any questions about your participation in the study, please contact Maher Almatar via phone: (03) 6226 1083 or email: malmatar@utas.edu.au. If you have any concerns of an ethical nature, or complaints about the manner in which the project is conducted, please contact Human Research Ethics Committee (Tasmania) Network (Ph: 03 6226 1956, Email: Adele.Kay@utas.edu.au).

Thank you for your assistance.

Yours sincerely,

Prof Gregory Peterson

Professor of Pharmacy and
Head of School

Mr Maher Almatar

PhD Candidate

Phone: 03 62261083

CONSENT FORM

MANAGEMENT OF PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA

1 I have read and understood the introductory letter for this study.

2 The nature of the study has been explained to me, and any questions that I have asked have been answered to my satisfaction.

4 I understand that the study involves an audio-recorded interview with a researcher about my experiences and opinions prescribing ceftriaxone for patients presenting with community acquired pneumonia.

5 I understand any information provided in this study will be kept strictly confidential.

6 I understand all the data collected in this study will be stored in a locked cabinet or password protected computer in the School of Pharmacy and will be securely destroyed five years after publication of the data.

7 I have been informed that the results of the study may not be of any direct benefit to me.

8 I agree that research data gathered for the study may be published provided that pseudonyms will be used to ensure no individual data is identified.

9 I agree to participate in this study and understand that I am free to withdraw at any time without explanation or prejudice and to withdraw any unprocessed data previously supplied.

Name: _____ Date: _____/_____/2012

Phone number: _____ *(to arrange a time and place for the interview)*

Signature: _____

If you would like to be informed of the overall results of the study please mark this box ☐

and a copy of the results will be forwarded to your workplace.

Statement by the researcher

I have explained this study and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of researcher: *Maher Almatar* Signature:

Date:

Appendix D. Interview Outlines

(N.B The schedule that follows is for a semi-structured interview, thus, the ordering of the questions will vary according to the way the interview evolves. Other questions not listed in this schedule may be asked to expand a topic if/as it emerges in the interview)

Before we start the interview, do you have any questions about the study?

I'd like to discuss the empirical use of ceftriaxone for patients presenting with community acquired pneumonia (CAP). I am interviewing emergency department medical staff in order to get a broad picture of what influences the decision to use ceftriaxone in this patient group.

In these interviews I am hoping to hear your experiences and opinions. All of the interviews will be treated confidentially and your name will not be used in any transcripts, reports or publications arising from this study.

Demographic/General Questions

1. What is your professional position (i.e. intern, registrar or consultant)
2. How many years have you been practising within emergency medicine?
3. Approximately how many cases of CAP are you involved with in an average month?

Interview Outline

4. What are your thoughts on empirical antibiotic management for patients presenting with CAP?
5. What source(s) of information do you often rely on when making decisions about CAP treatment?
6. What are your thoughts on the TG14 guidelines on CAP management? Any comments?
7. What leads you to prescribe ceftriaxone for patients presenting with CAP? i.e. What are the things you might consider when deciding to prescribe ceftriaxone for CAP patients?
8. Do you normally consult with any other doctors before making a decision to prescribe ceftriaxone for CAP?
9. What experiences do you feel have particularly influenced your prescribing practices in CAP?

Well those were all the questions I wanted to ask you. Is there anything you would like to add? Or anything you feel is important that we have left out?

Would you like to clarify any comments you have made?

Appendix E. Survey tool for antimicrobial pharmacists among Australian hospitals

Cover letter

Initiatives to optimise the empirical usage of antibiotics for patients with

Community-Acquired Pneumonia (CAP)

Dear Sir/Madam,

You are invited to take a part in a research study that aims to learn more about initiatives that have been performed to optimise CAP management in Australian hospital emergency departments. This study is being conducted by Maher Almatar (Pharmacy PhD student) under the supervision of Prof. Gregory Peterson (Professor of Pharmacy) and Mr Angus Thompson at the University of Tasmania.

Participation in this study involves the completion of an on-line questionnaire, which will take approximately 5 to 10 minutes. Once you have completed the questionnaire, you will be entered into a prize draw for the chance to win an iPad mini.

Your responses to the questionnaire will be totally confidential and anonymous, and all reported data will be aggregated. Details collected for entry into the prize draw are separate from the survey data. Should information collected through this study be published or presented at a conference, no participant or their institution will be identifiable.

It is important that you understand that your involvement is this study is entirely voluntary. While we would be pleased to have you participate, we respect your right to decline.

Should you have any questions about completing or participating in this study, please feel free to contact Maher Almatar on (03) 6226 1069 extension 8535 or via e-mail at malmatar@utas.edu.au.

This study has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study you should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote [H0013156].

Thank you for taking the time to consider this study. If you are willing to participate, please click the button below to proceed to the questionnaire.

Your completion and submission of the questionnaire will be taken as indicating your consent to participate in this study.

Thank you for your assistance.

Sincerely yours,

The questionnaire

This questionnaire aims to learn more about any initiatives that your institution/department has made to optimise the empirical usage of antibiotics for the management of community acquired pneumonia (CAP) in ED.

1- **Which state/territory is your institution in?**
   a. NSW
   b. VIC
   c. QLD
   d. SA
   e. WA
   f. TAS
   g. ACT
   h. NT

2- **Total number of hospital beds**
   a. Less than 100 beds
   b. 100-300 beds
   c. 301-500 beds
   d. More than 500 beds

3- **Do you have an antimicrobial stewardship program in your institution?**
   - No
   - Yes
   - No answer
     a. **If yes, in which year it was officially implemented?**
        i. 2011-2013
        ii. 2008-2010
        iii. before 2008

4- **Does your institution/department periodically monitor antibiotic use for the management of CAP in the emergency department?**
   - No
   - Yes

5- **Does your institution/department utilise guidelines for the management of CAP?**
   - No
   - Yes – Therapeutic Guidelines (Antibiotic)
   - Yes – local guideline

If yes,

   a. **What initiative/s does your institution/department use to promote uptake of the guidelines in the emergency department?**
      i. Group educational sessions
      ii. Academic detailing (one-on-one)
      iii. Drug restriction policy
      iv. Auditing and feedback

v. CAP management pathway
vi. Computer prompts or alerts/decision support
vii. None
viii. Others (please specify …….)

b. Which of the following do you think is/are effective to promote the uptake of the CAP guidelines? (Please indicate all that apply)

i. Group educational sessions
ii. Academic detailing (one-on-one)
iii. Drug restriction policy
iv. Auditing and feedback
v. CAP management pathway
vi. Computer prompts or alerts/decision support
vii. None
viii. Others (please specify …….)

c. Which ONE of the following do you think is the <u>most</u> effective to promote the uptake of the CAP guidelines?

i. Group educational sessions
ii. Academic detailing (one-on-one)
iii. Drug restriction policy
iv. Auditing and feedback
v. CAP management pathway
vi. Computer prompts or alerts/decision support
vii. None
viii. Others (please specify …….)

If no,

d. What initiative/s does your institution/department use to optimise the use of antibiotics for patients with CAP in the emergency department?

i. Group educational session
ii. Academic detailing (one-on-one)
iii. Drug restriction policy
iv. Auditing and feedback
v. CAP management pathway
vi. Computer prompts or alerts/decision support
vii. None
viii. Others (please specify …….)

e. Which of the following do you think is/are effective to optimise the use of antibiotics for patients with CAP?

i. Group educational session
ii. Academic detailing (one-on-one)

iii. Drug restriction policy
iv. Auditing and feedback
v. CAP management pathway
vi. Computer prompts or alerts/decision support
vii. None
viii. Others (please specify …….)

f. Which of the following do you think is the <u>most</u> effective to optimise the use of antibiotics for patients with CAP?

i. Group educational session
ii. Academic detailing (one-on-one)
iii. Drug restriction policy
iv. Auditing and feedback
v. CAP management pathway
vi. Computer prompts or alerts/decision support
vii. None
viii. Others (please specify …….)

6- Please rate your level of agreement with the following statement: "There is a need for additional education of ED staff on antimicrobial prescribing for CAP in my institution."

a. Strongly Agree
b. Agree
c. Natural
d. Disagree
e. Strongly disagree

7- What is/are the recommended tool/s to assess the severity of CAP in your department?

a. PSI
b. CURB65
c. SMARTCOP
d. CORB
e. None
f. Other (please specify……)

8- In general, would you please briefly describe the role of the antimicrobial stewardship program in your hospital's ED. (optional)

Thank You

Thank you for taking time out to participate in this survey. We truly value the information that you have provided.

Your survey has been submitted!

Please note that any information entered on this page is not linked to your responses in the survey.

If you wish to enter the prize draw to have the chance to win an iPad mini, please click on the "go to prize". Once you press that button, you will be asked to provide your name and Email address. This is optional, you can press the "no, thanks" button if you don't wish to enter into the prize draw.

Name:……

Email:……

Appendix F. RHH local CAP guidelines

Tasmanian Department of Health and Human Services
Royal Hobart Hospital
Clinical Guidelines

Tasmania

Southern Tasmania Area Health Service

Note: The electronic version of this document is the version currently in use. Any printed version can not be assumed to be current. Please remember to read our disclaimer.

ADULTS WITH COMMUNITY ACQUIRED PNEUMONIA – MANAGEMENT OF	GEN-1-0025

Background

Community acquired pneumonia (CAP) is commonly defined as an acute infection of the lower respiratory tract occurring in a patient who has not resided in a hospital in the previous 14 days. Empirical therapy for CAP differs from pneumonia acquired in hospital due to the different pathogens suspected.

Objective

This guideline is to assist in the selection of appropriate empirical antibiotics for patients with community acquired pneumonia. The recommendations assume immunocompetency and the absence of chronic suppurative lung disease, e.g. bronchiectasis.

Definitions

PNEUMONIA

Signs and symptoms consistent with an acute lower respiratory tract infection which may or may not include fever, rigors, new onset or worsening of cough, new sputum production or change in sputum colour if there is a chronic cough, shortness of breath and pleuritic pain

AND

New or worsening radiographic changes for which there is no other explanation

COMMUNITY ACQUIRED PNEUMONIA (CAP)

Pneumonia with symptom onset either before presentation to hospital or within 48 hours of hospital admission in an individual who has not been hospitalised in the previous 14 days.

PENICILLIN ALLERGY

1. Mild Allergy

The following represents a mild penicillin allergy:

- Delayed rash (non type 1 (non IgE-mediated))

2. Severe Allergy

The following represent a severe penicillin allergy or adverse drug reaction:

- Urticaria (hives), angioedema, bronchospasm or anaphylaxis within 1 hour of drug administration (type 1 (IgE mediated))
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Acute interstitial nephritis

Clinical Assessment of Severity

The RHH Adult CAP Guideline uses the **CORB** severity scoring system.

The **CORB** (**C**onfusion, **O**xygenation, **R**espiratory Rate, **B**lood pressure) **Score** is calculated at the time of presentation. It stratifies severity and helps guide therapy and the need for hospital admission.

Parameter		Score
Confusion	New onset or worsening of existing state if cognitive impairment is present	1
Oxygenation	PaO_2 less than or equal to 60mmHg OR O_2 saturations less than or equal to 90% on room air	1
Respiratory Rate	Greater than or equal to 30 breaths per min	1
Blood Pressure	Systolic BP less than or equal to 90mmHg OR diastolic less than or equal to 60mmHg	1

CORB Score Interpretation:

Score out of 4:

0	Mild pneumonia
1	Moderate pneumonia
2 or more	Severe pneumonia

Patient Triage

Criteria for outpatient treatment

- CORB score 0
- Ambulant, self-caring patients
- Able to take oral medications

There is no role for outpatient intravenous therapy.

Criteria for admission

- Mild pneumonia with significant co-morbidities and/or poor social support
- CORB score 1 or more (Moderate or severe pneumonia)
- Inability to tolerate oral antibiotics
- Patients who have deteriorated on outpatient therapy

Circumstances where discussion with the respiratory physician on-call is advised:

- CORB score of 2 or more (severe pneumonia)
- Multi-lobar involvement
- Underlying chronic respiratory disease (proven or suspected), e.g. COPD, pulmonary fibrosis
- Associated pleural effusion

Indications for referral to the intensive care team include:

- CORB score 2 or more (severe pneumonia)
- Severe/refractory hypoxemia (FiO_2 requirement 0.4 or above)
- Septic shock
- Multi-organ failure
- Marked agitation/delirium
- Loss of airway protection
- Complex co-morbidities
- Deterioration despite initial management

ADULTS WITH COMMUNITY ACQUIRED PNEUMONIA – MANAGEMENT OF

GEN-1-0025

Initial Management

The first priority is to stabilize the patient where possible:

1. Titrate supplementary oxygen to achieve saturations of 94-98% (88-92% if history of or risk factors for hypercapnia)
2. Fluid resuscitate if hypovolemic or hypotensive
3. Adequate analgesia as required

Appropriate antibiotic therapy should be initiated at the earliest possible opportunity, i.e. 1st doses should be administered in the initial assessing area (Emergency Department or Assessment and Planning Unit).

Antimicrobial therapy should not be delayed for the collection or reporting of pathology specimens

Empirical Management

Assessment of severity using the CORB score determines empirical therapy

Severity	First line therapy	Mild Penicillin Allergy	Severe Penicillin Allergy
Mild CORB = 0	Amoxicillin 1 gram orally 8-hourly OR If *Mycoplasma pneumoniae, Chlamydophila pneumoniae or Legionella* are suspected then use: Doxycycline 200mg stat then 100mg twice daily (If not tolerated then Clarithromycin 500mg twice daily)	Doxycycline 200mg stat then 100mg twice daily (If not tolerated then Clarithromycin 500mg twice daily)	Doxycycline 200mg stat then 100mg twice daily (If not tolerated then Clarithromycin 500mg twice daily)

Moderate CORB = 1	Benzylpenicillin 1.2 gram IV 6-hourly AND Doxycycline 200mg stat then 100mg twice daily (If Doxycyline not tolerated then use Clarithromycin 500mg twice daily)	Ceftriaxone 1 gram IV daily AND Doxycycline 200mg stat then 100mg twice daily (If Doxycycline not tolerated then use Clarithromycin 500mg twice daily)	Moxifloxacin 400mg orally daily
Severe CORB ≥ 2	Ceftriaxone 1 gram IV daily AND Azithromycin 500mg IV daily		Moxifloxacin 400mg IV or orally daily AND Azithromycin 500mg IV daily

Investigations

BASELINE BLOOD TESTS

- Full blood examination
- Electrolytes, urea and creatinine
- Liver function tests (to be considered at time of admission)
- C-reactive protein (to be considered at time of admission)

Arterial blood gases should be obtained in patients with severe pneumonia and/or at risk of hypercapnic respiratory failure (CO_2 retention)

ROUTINE MICROBIOLOGY TESTS

- Sputum microscopy, culture and sensitivity
- Blood cultures (Blood Culture Collection Protocol) in moderate to severe CAP
- Streptococcal and Legionella urinary antigens (moderate to severe CAP)

Other microbiological testing that may be considered includes:

- Nucleic acid testing (PCR) for influenza* or pertussis (*if meets ILI definition – Influenza-like illness and influenza – management 2012)
- Acute and convalescent sera for 'atypical pathogens'
- Mycoplasma IgM serology

- Legionella culture
- Further nucleic acid testing on discussion with Medical Microbiologist
- Ziehl-Nielsen (ZN) stain and culture for acid-fast bacilli in appropriate setting (elderly, immunosuppressed or immigrants from high prevalence countries)

Refinement of Antimicrobial Therapy and Switch to Oral Agents

Antimicrobial therapy may be altered with the availability of laboratory results and with clinical improvement of the patient. Direct and targeted therapy is recommended.

Patients should be stepped down from intravenous therapy when the following criteria are met:

1. Their vital signs are stable for at least 24 hours, i.e.
   - Temperature below 38 degrees centigrade
   - Heart rate less than 100 beats per minute
   - Respiratory rate less than 24 breaths/minute (spontaneously breathing patient)
   - Systolic blood pressure more than 90mmHg (or 100 if known hypertensive)

2. They are able to ingest* and absorb oral medications (*or have nasogastric tube in situ)

If the patient is not responding to treatment after 48 hours and no pathogen has been identified, consider the following:

- Revisiting patient history – with particular reference to travel, exposure to birds, risk factors for aspiration
- Respiratory team consultation

Duration of Antimicrobial Therapy

The following factors should be considered:

- Severity of infection
- The causative pathogen (known or assumed)
- The presence or absence of complications, e.g. complex parapneumonic effusion

Duration is left to the discretion of the treating team. Therapeutic Guidelines Antibiotic version 14 provides some guide.

Patients with CAP should be afebrile for 48–72 hours and show significant clinical improvement (with reduction in CORB score) before discontinuation of therapy. They should be treated for a minimum of 7 days in total.

Additional Considerations

- Smoking cessation advice should be offered to all smokers with CAP
- Nutritional support should be provided in prolonged illness
- Airway clearance techniques may be of benefit in patients with sputum who are having difficulty expectorating or in those with a pre-existing lung condition. Patients with uncomplicated CAP should not routinely be treated with traditional airway clearance techniques.
- Pneumococcal and Influenza vaccination should be recommended in at risk individuals according to Australian Immunization Handbook 8th Edition.

Infection Control

If suspicion of influenza, respiratory virus, *Bordetella pertussis* or tuberculosis refer to Reference Guide to Infection Control Management of Infectious Diseases or Influenza-like illness and influenza – management 2012.

References

1. Therapeutic Guidelines Antibiotic Version 14, Therapeutic Guidelines Limited 2010
2. Guidelines for the management of community acquired pneumonia in adults: update 2009. British Thoracic Society. Thorax Vol 64 sIII, 2009
3. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007 Mar 1;44 Suppl 2:S27-72.

Stakeholders

Department of Microbiology and Infectious Diseases, RHH
Department of Respiratory Medicine, RHH
Department of Emergency Medicine, RHH

ADULTS WITH COMMUNITY ACQUIRED PNEUMONIA – MANAGEMENT OF

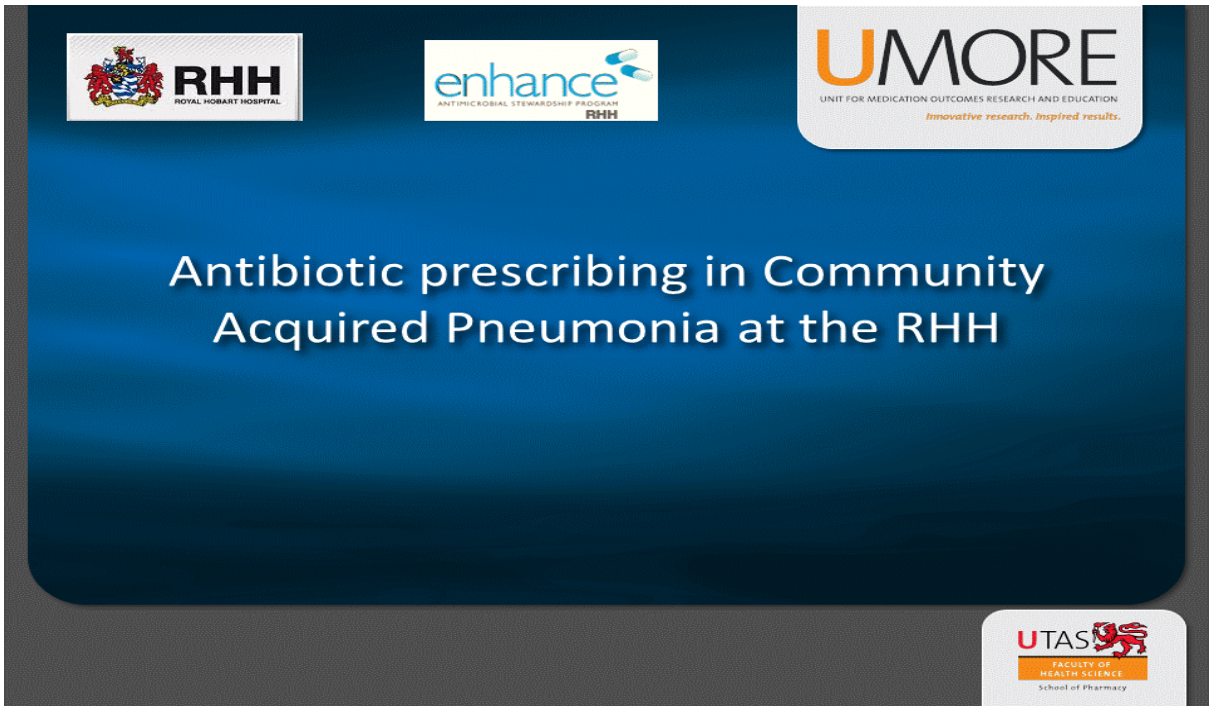
GEN-1-0025

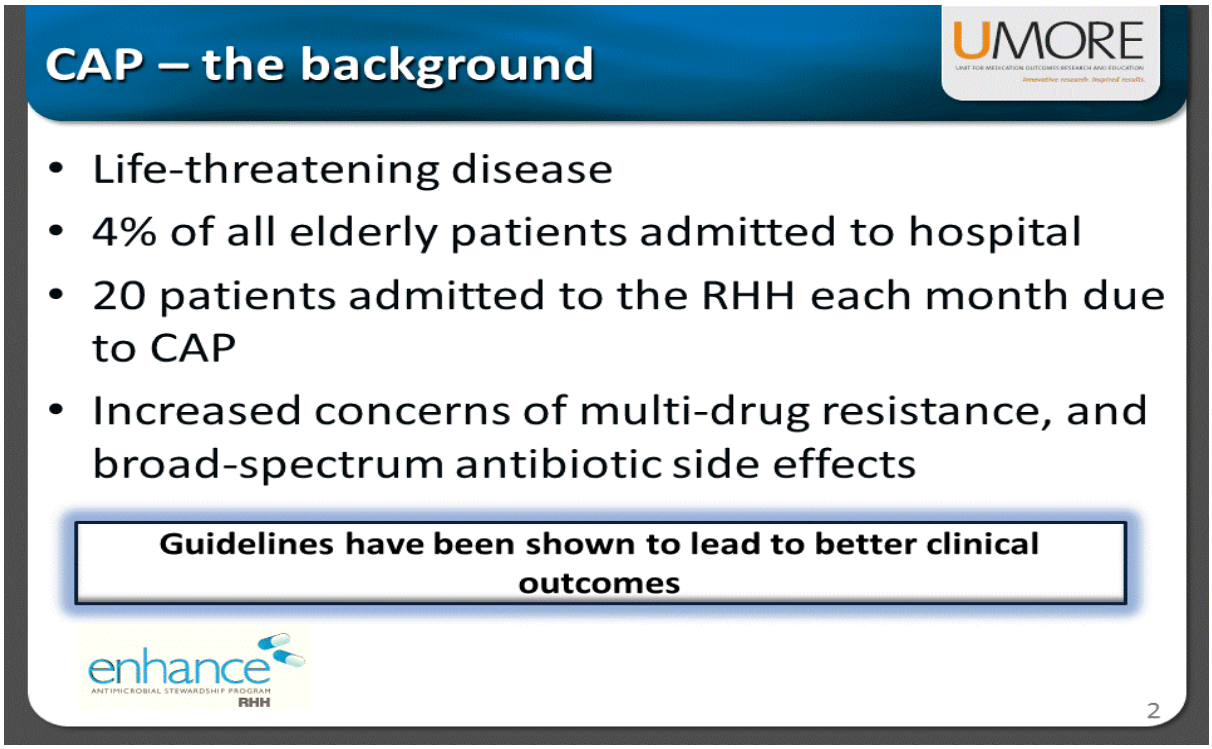
Department of General Medicine, RHH
Department of Critical Care Medicine
Pharmacy Department, RHH

Key Words - Intranet Search Function

1. CORB Score
2. Influenza
3. CAP

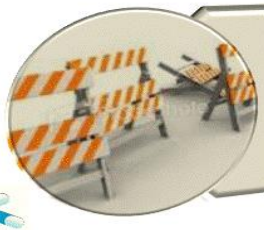
Appendix G. CAP power point slides for educational sessions





This study has two parts

Review of CAP management



Barrier survey

3

Methods

- Retrospective audit for 10 months after TG14 release in June 2010
- Included all patients (≥ 18 yo) who were diagnosed with pneumonia and received antibiotic therapy within 24 hours of presentation (whether admitted or not)
- Exclusion criteria:
  - Admission from nursing home
  - Hospital admission in the previous 14 days
  - Immunosuppression

5

Review of CAP management

Methods

- Retrospective audit for 10 months after TG14 release in June 2010
- Included all patients (≥ 18 yo) who were diagnosed with pneumonia and received antibiotic therapy within 24 hours of presentation (whether admitted or not)
- Exclusion criteria:
  - Admission from nursing home
  - Hospital admission in the previous 14 days
  - Immunosuppression

5

Methods continued

- Review of
  - Medical notes
  - Radiology reports
  - Laboratory tests

→ In order to calculate SMARTCOP and CORB to assess the severity of CAP

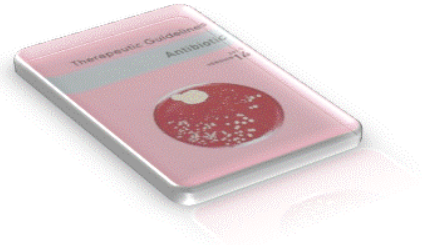
  - Drug charts

→ To identify the initial antibiotic regimen

6

Key focus areas

- Empirical therapy for patients diagnosed with CAP
- The documented use of severity tool(s) for severity assessment
- Adherence to the Antibiotic Therapeutic Guidelines (TG14)



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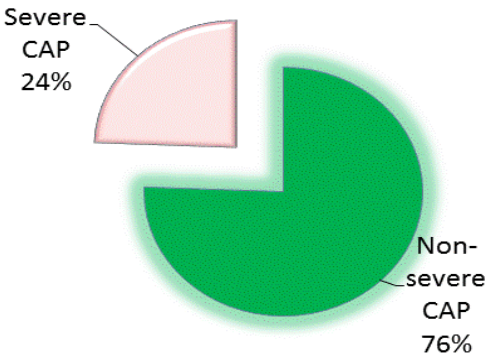
Severity Profile of Population

When the severity of CAP was calculated using SMARTCOP/CORB tools the vast majority of patients were found to have **non-severe CAP**



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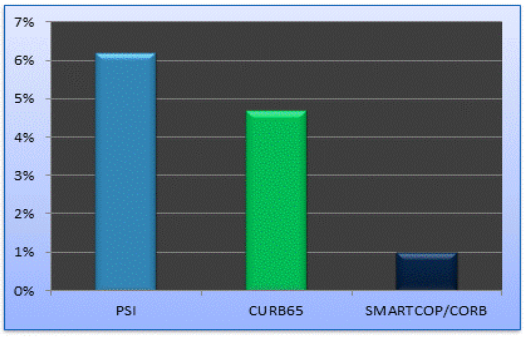
Severity Assessment Tools

- Only 12% of patients with CAP had a documented severity assessment in their medical records
- A range of severity assessment tools were used:
  - PSI
  - CURB65
  - SMARTCOP/CORB



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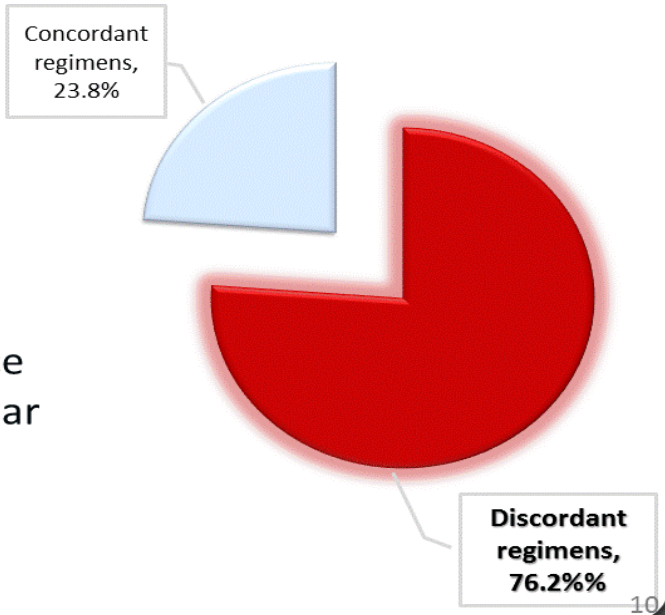
Adherence to TG14

- More than three-quarters of patients with CAP received discordant antibiotic regimen
- Levels of concordance with TG14 were similar in severe and non-severe CAP



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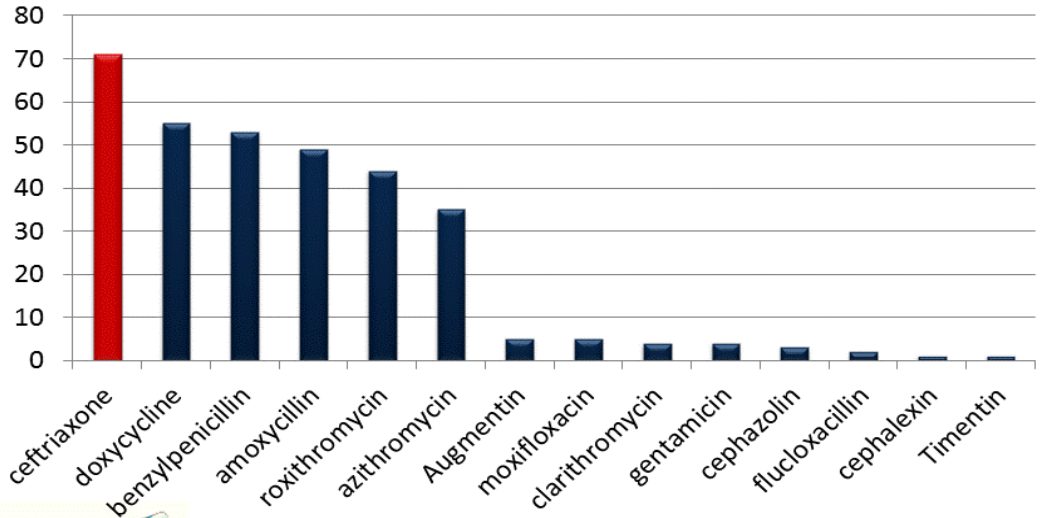
Frequency of used antibiotics



Empirical antibiotic regimens

Empirical antibiotic regimens used for patients with CAP.

Antibiotic regimen		Non-severe CAP (n = 146)	Severe CAP (n =47)	Total
Penicillin-based therapy* N = 103	Alone	20	0	20
	Azithromycin	5	1	6
	Roxithromycin	21	6	27
	Clarithromycin	1	1	2
	Doxycycline	38	7	45
	Aminoglycosides	1	2	3
Ceftriaxone-based therapy N = 71	Alone	**15**	7	22
	Azithromycin	**12**	14	26
	Roxithromycin	**12**	4	16
	Doxycycline	**5**	2	7
Other-based therapy N = 19		16	3	19

*(benzylpenicillin, amoxicillin or ampicillin)

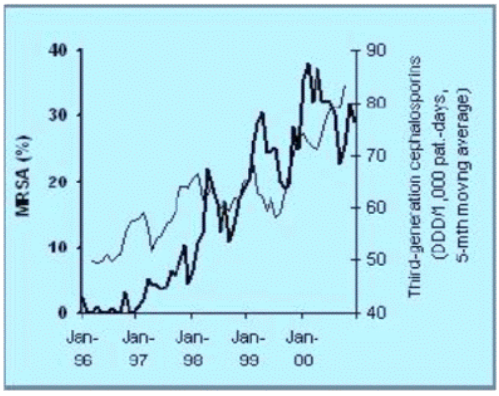
Ceftriaxone in non-severe CAP

- One of the most significant findings was that ceftriaxone is widely used in non-severe CAP
- TG14 recommends penicillin-based therapy, not ceftriaxone in these cases

Antibiotic regimen		Non-severe CAP	Severe CAP	Total
Ceftriaxone-based therapy N = 71	Alone	15	7	22
	Azithromycin	12	14	26
	Roxithromycin	12	4	16
	Doxycycline	5	2	7

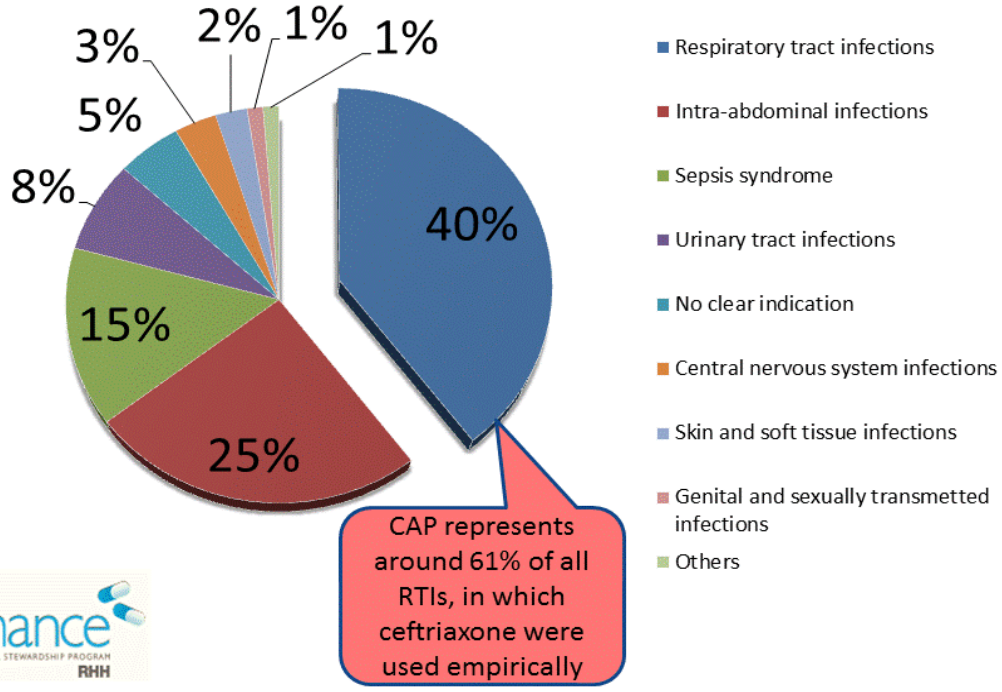
Ceftriaxone use and bacterial resistance

There is a strong relationship between the use of third generation cephalosporins, such as ceftriaxone, and the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA)



Source: Monnet DL.et al. Emerg Infect Dis 2004;10:1432-1441

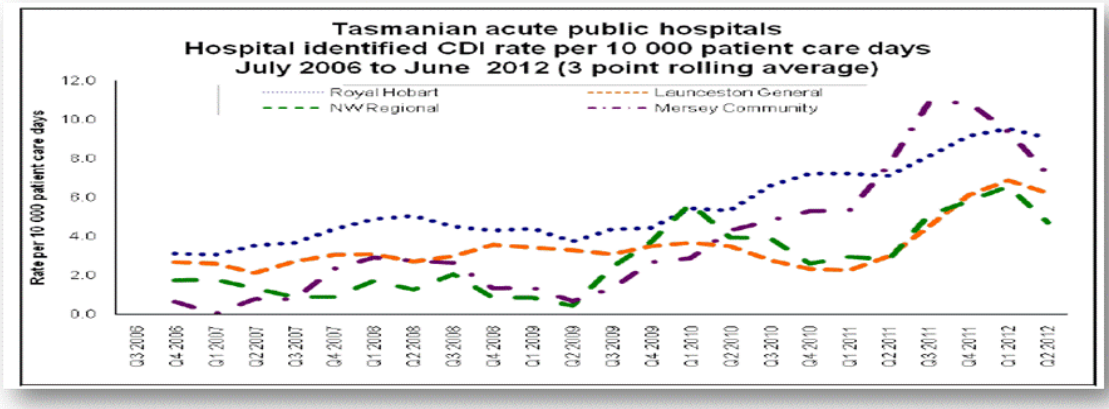
Site of infections and ceftriaxone empirical use (n=247) at the RHH



Ceftriaxone use and *C. difficile* infection (CDI)

- Third generation cephalosporins, such as ceftriaxone, are independently associated with the development of CDI
- Limiting ceftriaxone usage has led to significant reduction of CDI in elderly patients.

Sources: Vivian GL.et al. N Eng J Med 2005;353:2442-2449.
Khan R and Cheesbrough J. J Hosp Infect 2003;54:104-108.



It is evident that the number of incidence of CDI at the RHH are increased markedly over the period time between 2006 to 2012.

Aetiology of CAP in Australia

- In one largest prospective study of the aetiology of CAP in Australia, it was found that the most common identified bacterial pathogen was *Streptococcus pneumoniae*.
- Only a minority of cases were caused by Gram Negative Enteric Bacteria (GNEB) *or Staphylococcus aureus,* even in more severe cases.

Broad-spectrum antibiotics, such as ceftriaxone, are not necessary for the vast majority of Australian patients with CAP

Source: Patrick GP. et al. Clin Infect Dis 2008; 46:1513-1521.

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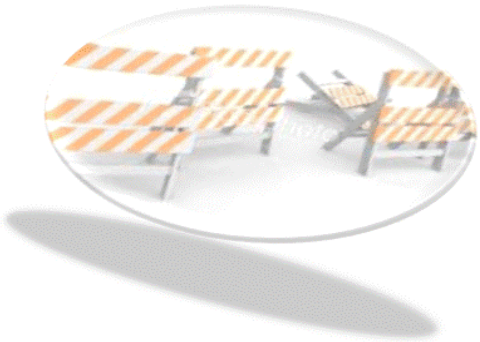
Objective

- To identify barriers that might lead to poor adherence with regard to the empirical management of CAP.



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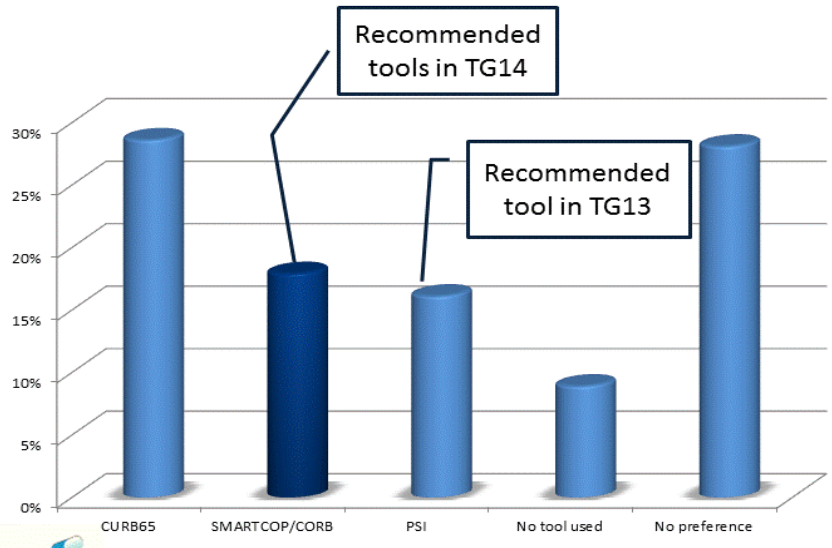
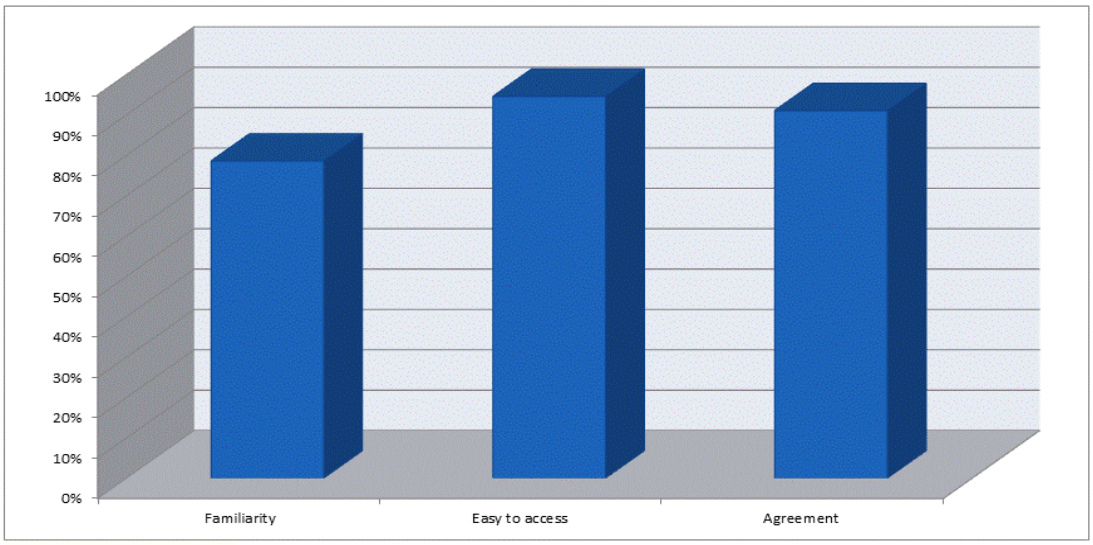
Self-reported use of severity tool(s)



Self-Reported familiarity with, Accessibility to and Agreement with TG14



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Doctors' views on the reasons that hinder other doctors from adhering to TG14

Barriers due to knowledge

- Lack of awareness (39.3%)

Barriers due to Attitude

- Not expected to follow the guidelines (23.8%)

External factors

- Influence of senior doctors (46.4%)
- Existence of other guidelines (28.6%)

The RHH hospital CAP guidelines

The RHH CAP (adult) guidelines have been developed by and have the support of the Antimicrobial Stewardship Committee and the following teams; Infectious Diseases, Respiratory Medicine, Emergency Medicine and Pharmacy

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Pneumonia

- Signs and symptoms consistent with an acute lower respiratory tract infection which may or may not include fever, rigors, new onset or worsening of cough, new sputum production or change in sputum colour if there is a chronic cough, shortness of breath and pleuritic pain

AND

- New or worsening radiographic changes for which there is no other explanation

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CAP

- Pneumonia with symptom onset either before presentation to hospital or within 48 hours of hospital admission in an individual who has not been hospitalised in the previous 14 days.

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- The RHH CAP guidelines consist of two main recommendations with regard to empirical treatment:
  - The recommended tool to assess the severity of CAP (CORB)
  - The recommended antibiotic regimen based on the severity

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Severity assessment (CORB)

variable	Definition	score
Confusion	New onset or worsening of existing state if cognitive impairment present	1 point
Oxygenation	PaO2 ≤ 60 mm or O2 saturation ≤ 90%	1 point
Respiratory rate	≥ 30 breath / min	1 point
Blood pressure	Systolic BP ≤ 90 mm Hg or Diastolic BP ≤ 60 mm Hg	1 point

Mild CAP = 0 points
Moderate CAP = 1 point
Severe CAP ≥ 2 points

- Only four variables
- Each variable values 1 point
- No need for lab test
- Recommended in TG14

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The recommended antibiotic regimens

CAP severity	Preferred antibiotic regimen
Mild CAP (CORB score = 0)	Amoxycillin 1 gram orally 8 hourly.
Moderate CAP (CORB score = 1)	Benzylpenicillin 1.2 gram IV 6 hourly AND Doxycycline 200 mg stat then 100 mg twice daily.
Severe CAP (CORB score ≥ 2)	Ceftriaxone 1 gram IV daily AND Azithromycin 500 mg daily

Ceftriaxone is reserved for patients with severe CAP

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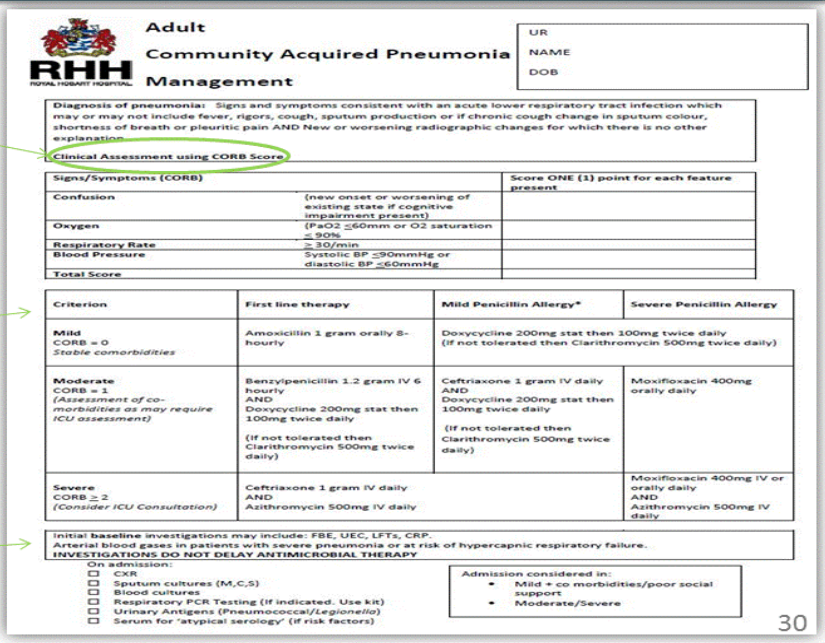
CAP (Adult) Tool

CORB score

Empirical therapy

Investigations



Adult
Community Acquired Pneumonia
Management

UR
NAME
DOB

Diagnosis of pneumonia: Signs and symptoms consistent with an acute lower respiratory tract infection which may or may not include fever, rigors, cough, sputum production or if chronic cough change in sputum colour, shortness of breath or pleuritic pain AND New or worsening radiographic changes for which there is no other explanation

Clinical Assessment using CORB Score

Signs/Symptoms (CORB)		Score ONE (1) point for each feature present
Confusion	(new onset or worsening of existing state if cognitive impairment present)	
Oxygen	(PaO2 ≤60mm or O2 saturation ≤ 90%	
Respiratory Rate	≥ 30/min	
Blood Pressure	Systolic BP <90mmHg or diastolic BP ≤60mmHg	
Total Score		

Criterion	First line therapy	Mild Penicillin Allergy*	Severe Penicillin Allergy
Mild CORB = 0 *Stable comorbidities*	Amoxicillin 1 gram orally 8-hourly	Doxycycline 200mg stat then 100mg twice daily (If not tolerated then Clarithromycin 500mg twice daily)	
Moderate CORB = 1 *(Assessment of co-morbidities as may require ICU assessment)*	Benzylpenicillin 1.2 gram IV 6 hourly AND Doxycycline 200mg stat then 100mg twice daily (If not tolerated then Clarithromycin 500mg twice daily)	Ceftriaxone 1 gram IV daily AND Doxycycline 200mg stat then 100mg twice daily (If not tolerated then Clarithromycin 500mg twice daily)	Moxifloxacin 400mg orally daily
Severe CORB ≥ 2 *(Consider ICU Consultation)*	Ceftriaxone 1 gram IV daily AND Azithromycin 500mg IV daily		Moxifloxacin 400mg IV or orally daily AND Azithromycin 500mg IV daily

Initial baseline investigations may include: FBE, UEC, LFTs, CRP.
Arterial blood gases in patients with severe pneumonia or at risk of hypercapnic respiratory failure.
INVESTIGATIONS DO NOT DELAY ANTIMICROBIAL THERAPY

On admission:
- ☐ CXR
- ☐ Sputum cultures (M,C,S)
- ☐ Blood cultures
- ☐ Respiratory PCR Testing (If indicated. Use kit)
- ☐ Urinary Antigens (Pneumococcal/*Legionella*)
- ☐ Serum for 'atypical serology' (if risk factors)

Admission considered in:
- Mild + co morbidities/poor social support
- Moderate/Severe

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- CORB allows severity of CAP to be easily assessed as only four clinical parameters are required
- The vast majority of cases of CAP are non-severe (CORB 0 or 1) and first line treatment for these cases is penicillin based therapy, not ceftriaxone
- Ceftriaxone is only a first line therapy for patients with CORB score ≥ 2

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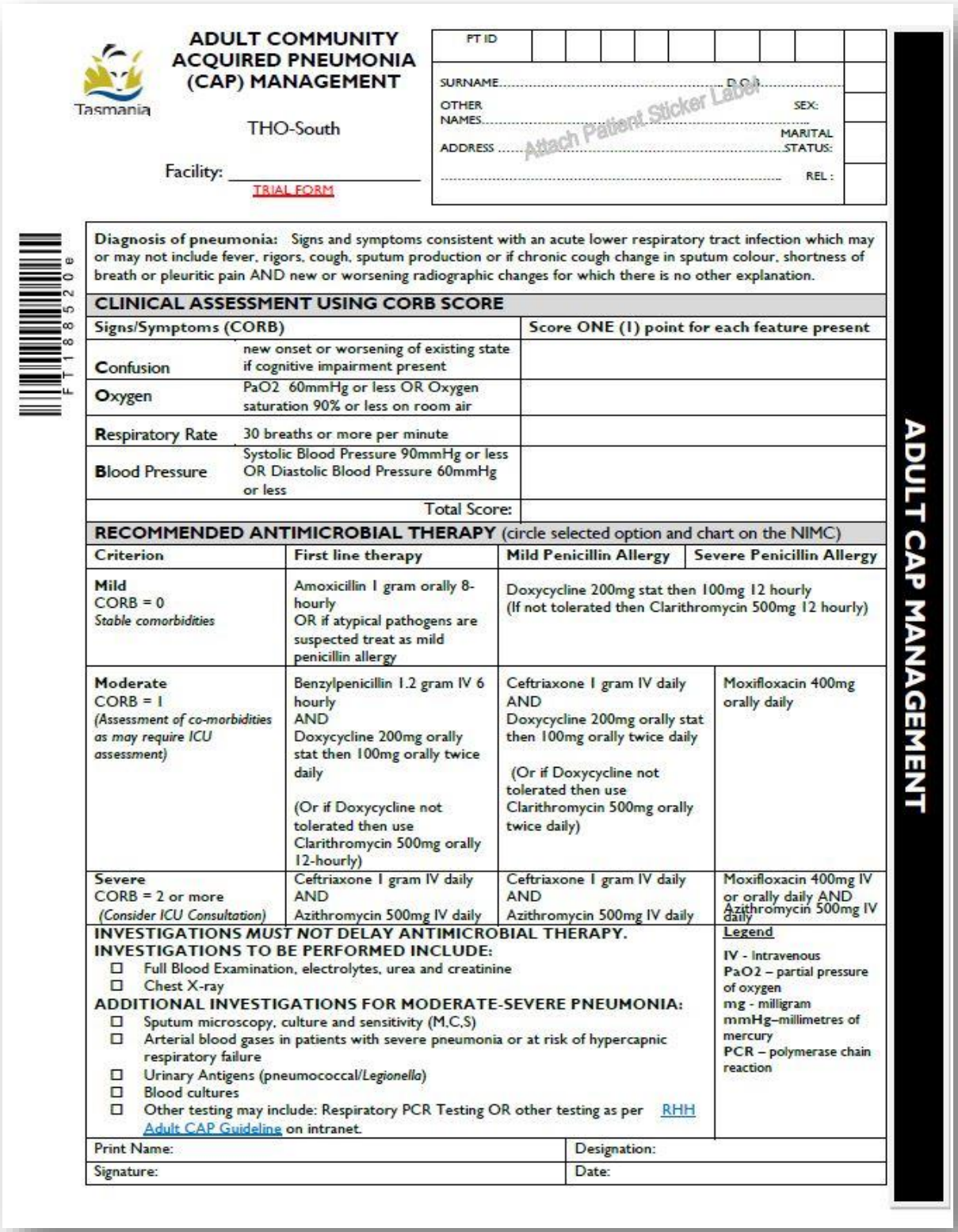
Thank you

- Comments/suggestions?
- Contacts:
  - Dr Tara Anderson (ID Physician)
  - Duncan McKenzie(Pharmacy Manager)
  - Dr David Stock (Respiratory Physician)

Appendix I: CAP clinical pathway component of intervention, as provided to ED.



ADULT COMMUNITY ACQUIRED PNEUMONIA (CAP) MANAGEMENT

Tasmania

THO-South

Facility: _____

TRIAL FORM

PT ID

SURNAME..... D.O.B.....

OTHER NAMES..... SEX:

ADDRESS ..... MARITAL STATUS:

..... REL :

Attach Patient Sticker Label

ADULT CAP MANAGEMENT

Diagnosis of pneumonia: Signs and symptoms consistent with an acute lower respiratory tract infection which may or may not include fever, rigors, cough, sputum production or if chronic cough change in sputum colour, shortness of breath or pleuritic pain AND new or worsening radiographic changes for which there is no other explanation.

CLINICAL ASSESSMENT USING CORB SCORE

Signs/Symptoms (CORB)		Score ONE (1) point for each feature present
Confusion	new onset or worsening of existing state if cognitive impairment present	
Oxygen	PaO2 60mmHg or less OR Oxygen saturation 90% or less on room air	
Respiratory Rate	30 breaths or more per minute	
Blood Pressure	Systolic Blood Pressure 90mmHg or less OR Diastolic Blood Pressure 60mmHg or less	
	Total Score:	

RECOMMENDED ANTIMICROBIAL THERAPY (circle selected option and chart on the NIMC)

Criterion	First line therapy	Mild Penicillin Allergy	Severe Penicillin Allergy
Mild CORB = 0 *Stable comorbidities*	Amoxicillin 1 gram orally 8-hourly OR if atypical pathogens are suspected treat as mild penicillin allergy	Doxycycline 200mg stat then 100mg 12 hourly (If not tolerated then Clarithromycin 500mg 12 hourly)	
Moderate CORB = 1 *(Assessment of co-morbidities as may require ICU assessment)*	Benzylpenicillin 1.2 gram IV 6 hourly AND Doxycycline 200mg orally stat then 100mg orally twice daily (Or if Doxycycline not tolerated then use Clarithromycin 500mg orally 12-hourly)	Ceftriaxone 1 gram IV daily AND Doxycycline 200mg orally stat then 100mg orally twice daily (Or if Doxycycline not tolerated then use Clarithromycin 500mg orally twice daily)	Moxifloxacin 400mg orally daily
Severe CORB = 2 or more *(Consider ICU Consultation)*	Ceftriaxone 1 gram IV daily AND Azithromycin 500mg IV daily	Ceftriaxone 1 gram IV daily AND Azithromycin 500mg IV daily	Moxifloxacin 400mg IV or orally daily AND Azithromycin 500mg IV daily

INVESTIGATIONS *MUST NOT* DELAY ANTIMICROBIAL THERAPY.

INVESTIGATIONS TO BE PERFORMED INCLUDE:

- ☐ Full Blood Examination, electrolytes, urea and creatinine
- ☐ Chest X-ray

ADDITIONAL INVESTIGATIONS FOR MODERATE-SEVERE PNEUMONIA:

- ☐ Sputum microscopy, culture and sensitivity (M,C,S)
- ☐ Arterial blood gases in patients with severe pneumonia or at risk of hypercapnic respiratory failure
- ☐ Urinary Antigens (pneumococcal/*Legionella*)
- ☐ Blood cultures
- ☐ Other testing may include: Respiratory PCR Testing OR other testing as per RHH Adult CAP Guideline on intranet.

Legend

IV - Intravenous
PaO2 – partial pressure of oxygen
mg - milligram
mmHg–millimetres of mercury
PCR – polymerase chain reaction

Print Name:	Designation:
Signature:	Date:

TIME TO ANTIBIOTICS IS PARAMOUNT. ANTIBIOTIC ADMINISTRATION WITHIN 4 HOURS OF ARRIVAL IS ASSOCIATED WITH DECREASED MORTALITY AND LENGTH OF STAY.

Penicillin Hypersensitivity/Severe life-threatening penicillin allergy

Severe life-threatening penicillin allergy, or Type I hypersensitivity, are Immunoglobulin E mediated reactions resulting in the release of histamines and other mediators from mast cells and basophils. Reactions occur immediately to one hour after exposure, and are characterised by urticaria, angioedema, bronchospasm and anaphylaxis.

Discussion with Respiratory Team for admission is recommended in:

- Moderate or Severe pneumonia
- Mulitlobar pneumonia
- Significant parapneumonic effusion
- Patients with pneumonia who are well known to respiratory team.

Indications for referral to the intensive care team include:

- CORB score 2 or more (severe pneumonia)
- Severe/refractory hypoxemia (fraction of inspired oxygen requirement 0.4 or above)
- Septic shock
- Multi-organ failure
- Marked agitation/delirium
- Loss of airway protection
- Complex co-morbidities

'Atypical' pneumonia

Atypical pneumonia includes: *Chlamydophilia/Chlamydia* species, *Mycoplasma pneumoniae* and *Legionella* species).

Serum for atypical serology (*Chlamydophilia/Chlamydiai* species, *Mycoplasma pneumoniae* and *Legionella* species) will only be tested with the receipt of convalescent serum in the laboratory (taken at 2-4 weeks post illness) or in discussion with the Medical Microbiologist.

Less common but important aetiology:

Legionella diagnosis has important public health implications. Consider and ensure testing if concern especially if renal failure and/or gastrointestinal symptoms are present.

PLEASE REFER TO THE MANAGEMENT OF ADULTS WITH COMMUNITY ACQUIRED PNEUMONIA GUIDELINE ON THE INTRANET FOR THE COMPLETE GUIDELINE.

Appendix J. Samples of a detailed monthly feedback to the ED staff.

Random cases August 08	Documented usage of CORB	Documented severity of CAP	Severity based on CORB	Empirical ABX	Concordant with hospital guidelines	CXR change	Comments
Case 1	Clinical pathway utilised	Yes	Severe	Ceftriaxone 1 g IV + Azithromycin 500 mg IV	Yes	No	
Case 2	Clinical pathway utilised	Yes	Severe	Ceftriaxone 1 g IV and Azithromycin 500 mg IV	Yes	No	Penicillin allergy
Case 3	Clinical pathway utilised	Yes	Mild	Amoxycillin 1 g PO and Doxycycline	No	No	
Case 4	Clinical pathway utilised	Yes	Mild	Amoxycillin 1 g PO	Yes	No	
Case 5	No	Yes	Mild	Benzylpenicillin 1.2 g IV	No	No	
Case 6	No	No	Mild	Ceftriaxone 1 g IV and Doxycycline 200 mg PO	No	Yes	
Case 7	No	No	Mild	Amoxycillin 1 g IV	No	No	Discordant route of administration
Case 8	Clinical pathway utilised	Yes	Moderate	Ceftriaxone 1 g IV and Doxycycline 200 mg PO	Yes	Yes	Penicillin allergy
Case 9	No	No	Severe	Ceftriaxone 1 g IV and Azithromycin 500 mg IV	Yes	Yes	
Case 10	No	No	Mild	Amoxycillin 1 g PO	Yes	No	

Appendix K. Ceftriaxone Usage at the RHH (Auditing tool).

Patient's study number:		
Gender:	Male ☐	Female ☐
Age:	**Wight:**	
Allergic to Penicillin:	Yes ☐	No ☐
Medical history, CXR or Lab results (if required in TG14 guidelines):		
Ceftriaxone-based therapy regimen:		
Information needed for patients admitted to the ED		
Ceftriaxone received at ED:	Yes ☐	No ☐
Patient admitted:	Yes ☐	No ☐
Ceftriaxone continued after admission:	Yes ☐	No ☐
Ceftriaxone indication:		
Ceftriaxone use	empirical ☐	
Details of microbiological testing	directed ☐ Organism……..	
	prophylaxis ☐	
Dosage:		
Duration of ceftriaxone therapy:		

Is the use of ceftriaxone indicated in the TG14?	Yes	☐	No	☐
If yes, is the ceftriaxone-based therapy consistent with TG14?	Yes	☐	No	☐
Prescribed by:	Intern	☐		
	Resident	☐		
	Registrar	☐		
	Specialist/Consultant	☐		
Outcome: Discharged (LOS) Died Comments:				

Appendix L. Ethical approvals

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

29 April 2011

Professor Gregory Peterson
School of Pharmacy
Private Bag 26
Hobart TAS 7000

Dear Professor Peterson,

REF NO: H11729
TITLE: The use of antibiotic therapy for the management of lower respiratory tract infection in patients at the Royal Hobart Hospital

- *Application Form- Low Risk*
- *Data Form*

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on **27 April 2011.**

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct Human Research* (NHMRC 2007).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4)All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

Tasmania
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(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **27 April 2012.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 1956.

Yours sincerely

Adele Kay
Health and Medical HREC Ethics Officer
On behalf of the Executive Officer
HREC (Tas) Network

Tasmania
Explore the possibilities

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

22 December 2011

Professor Gregory Peterson
School of Pharmacy
Private Bag 26
Hobart TAS 7000

Dear Professor Peterson,

REF NO: H11729
TITLE: The use of antibiotic therapy for the management of lower respiratory tract infection in patients at the Royal Hobart Hospital

- *Addition of survey to identify the barriers that hinder physicians from adhering to the TG14 guideline regarding the management of community acquired pneumonia (CAP)*
- *Amendment to add additional site North West Regional Hospital*

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above amendment documentation on **16 December 2011**.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on Ethical Conduct in Human Research* (NHMRC 2007).

Should you have any queries please do not hesitate to contact me on (03) 6226 1956.

Yours sincerely,

Akay

Adele Kay
Executive Officer, Health and Medical HREC
Human Research Ethics Committee (TAS) Network

Tasmania
Explore the possibilities

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

24 September 2012

Professor Gregory Peterson
C/- Pharmacy

Sent via email

Dear Professor Peterson

REF NO: H0012809
TITLE: The use of ceftriaxone at the Royal Hobart Hospital's emergency department for patients who present with community acquired pneumonia: a qualitative investigation

Low Risk Application Form
Interview outline
Letter of Invitation

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on **23 September 2012**.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC.

(3) Section 5.5.3 of the National Statement states:

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http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 23 September 2013. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Lauren Townsend
Ethics Administrator
Office of Research Services
Tel: +61 (0)3 6226 2764
Email: Lauren.Townsend@utas.edu.au
University of Tasmania, Private Bag 01 Hobart Tas 7001

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
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HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

19 June 2012

Prof Gregory Peterson
School of Pharmacy
University of Tasmania

Sent via email

Dear Professor Peterson,

REF NO: H12489
TITLE: The use of ceftriaxone at the Royal Hobart Hospital

- *Application Form- Low Risk*
- *Privacy Form*

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation following its meeting on **28 May 2012.**

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC.

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regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.research.utas.edu.au/human_ethics/medical_forms.htm

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(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **1 June 2013.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 1956.

Yours sincerely

Adele Kay
Ethics Officer
Health and Medical Human Research Ethics Committee
Human Research Ethics Committee (Tas) Network

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
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HUMAN
RESEARCH
ETHICS
COMMITTEE
(TASMANIA)
NETWORK

UTAS

28 May 2013

Professor GM Peterson
C/- Faculty of Health Science

Sent via email

Dear Professor Peterson

REF NO: **H0012489**
TITLE: **The use of ceftriaxone at the Royal Hobart Hospital**

- *Collection of follow up data*

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above amendment documentation on 27 May 2013.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on Ethical Conduct in Human Research* (NHMRC 2007).

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Lauren Black
Ethics Administrator
Office of Research Services
Tel: +61 (03) 6226 2764
Email: lauren.black@utas.edu.au
University of Tasmania
Private Bag 01 Hobart Tas 7001

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

28 November 2012

Professor Gregory Peterson
C/- Pharmacy

Sent via email

Dear Professor Peterson

REF NO: H0012810
TITLE: An intervention to improve the use of antibiotics for the management of community acquired pneumonia

Human Research Ethics Committee (Tas) Network Privacy Form
Application Form Low Risk

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on **28 November 2012**.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC.

(3) Section 5.5.3 of the National Statement states:

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(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 28 November 2013. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Lauren Townsend
Ethics Administrator
Office of Research Services
Tel: +61 (0)3 6226 2764
Email: Lauren.Townsend@utas.edu.au
University of Tasmania, Private Bag 01 Hobart Tas 7001

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

26 April 2013

Professor Gregory Peterson
C/- UTas School of Pharmacy

Sent via email

Dear Professor Peterson

REF NO: H0013156
TITLE: Optimising the empirical usage of antibiotics for patients presenting to hospital with community acquired pneumonia

Application Form Low Risk
Information Sheet dated 4 April 2013

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on **26 April 2013** to be conducted at the following site(s):

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

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(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Lauren Black
Ethics Administrator
Office of Research Services
Tel: +61 (03) 6226 2764
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University of Tasmania
Private Bag 01 Hobart Tas 7001